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(54) Title: TANKYRASE2 MATERIALS AND METHODS

(57) Abstract: The invention provides novel tankyrase polypeptides designated tankyrase2, polynucleotides encoding the polypep-
tides, expression constructs comprising the polynucleotides, and host cells transformed with the expression constructs. Also pro-
vided are methods for producing the tankyrase2 polypeptides, antibodies that are immunoreactive with the tankyrase2 polypeptides.
In addition, there are provided methods for identifying specific binding partners of tankyrase2, and more particularly methods for
identifying binding partners that modulate biological activity of tankyrase2. Methods of modulating biological activity of tankyrase2
in vitro and *in vivo* are also provided.

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TANKYRASE2 MATERIALS AND METHODS

This application claims the benefit of United States Provisional Application Serial No. 60/141,582, filed June 29, 1999.

5 The present invention relates generally to a novel tankyrase polypeptide having poly ADP-ribosylation activity, to polynucleotides encoding the polypeptide, and to methods of using such materials.

BACKGROUND OF THE INVENTION

10 The ends of eukaryotic chromosomes (telomeres) are characterized by simple repeat DNA sequences. The length and sequence of the repeats varies from species to species but the importance of telomeres is universal in organisms with linear chromosomes. Telomeres protect the ends of the chromosomes and ostensibly function to prevent recombination of chromosome ends, which leads to chromosomal fusion and instability. In addition, there is considerable evidence that the length of the telomere repeats determines the ability of a cell to divide or perhaps even to survive.

15 The telomeres of cultured primary human fibroblasts become progressively shorter with each cell division in the absence of an active mechanism to regenerate telomere length [Harley et al., *Nature* 345:458-60 (1990)]. At some critical stage of telomere shortening, these cells are no longer able to divide and enter a state known as cellular senescence. Thus, in human primary fibroblasts at least, telomere length functions as a biological clock to monitor cellular aging and regulate longevity.

20 The observation that telomere length regulates cellular aging prompted the hypothesis that telomere regulation may also be critical for organismal aging. Mice that are unable to replicate telomeres show characteristics of premature aging after the third generation. These characteristics include premature graying, decreased cell division capacity, impaired wound healing, and increased cancer incidence amongst others. Thus, regulation of telomere structure may be critical for some of the characteristics associated with aging. Drugs that modulate the regulation of telomere structure thus may have utility in treatment of age-related syndromes or in cases of

25 genetically determined premature aging syndromes.

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Only recently has some of the machinery that replicates telomeres been described. This machinery, collectively referred to as the telomerase complex, consists of several proteins that replicate the telomeres and protect the telomere structure from DNA repair, which otherwise might treat telomeres as damaged DNA and affect end joining or recombination thus destroying the integrity of the chromosome. Telomerase is the replicative component of the telomerase complex and is a DNA polymerase that features an integral RNA molecule that serves as the template for the addition of the repetitive sequences [for a review, see Greider, *Ann Rev Biochem* 65:337-65 (1996)]. The observation that telomerase activity is essential for continued cell division suggests that inappropriate telomerase activity may be, in some instances, a contributing factor in the oncogenic transformation of cells. Forced expression of telomerase does not in and of itself cause oncogenic transformation but the fact that cells overexpressing telomerase have apparently unlimited capacity to replicate suggests that inappropriate expression of telomerase may be one step in a multi-step process of oncogenic transformation. In addition, numerous studies have shown that telomerase activity is higher in tumor tissue than most normal tissues suggesting that increased telomerase activity may be essential for tumor growth [for reviews, see Bacchetti, *Cancer Surv* 28:197-216 (1996); and Harley et al., *Cold Spring Harbor Symp Quant Biol* 59:307-15(1994)].

Two telomere-specific DNA binding proteins, designated TRF1 and TRF2 have also been shown to be important for maintenance of telomeres [Chong et al., *Science* 270:1663-7 (1995); van Steensel et al., *Cell* 92:401-13 (1998)]. TRF1 has a critical role in the regulation of telomere length while TRF2 seems to be important for protecting chromosome ends. Both molecules contain DNA binding domains and dimerization domains and both appear to function as homodimers. Binding of TRF1 to telomere repeats inhibits the function of telomerase thus contributing to telomere shortening during replication [van Steensel and de Lange, *Nature* 385:740-3 (1997)].

An additional molecule, tankyrase, has been identified which modifies TRF1 by the addition of polymers of ADP-ribose [Smith et al., *Science* 282:1484-7 (1998)]. Tankyrase is structurally and functionally related to the Poly(ADP-Ribose) Polymerase (PARP) molecule, which modifies proteins by the addition of ADP-ribose

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polymers [for review see Alvarez-Gonzalez et al., *Mol Cell Biochem* 138:33-7 (1994)]. The structural relationship to PARP exists in a putative catalytic domain of tankyrase that has extensive amino acid sequence similarity to PARP. In addition, tankyrase contains a sterile alpha motif (SAM) and 24 ankyrin repeats. These structures are typically involved in protein/protein interactions and at least a portion of the ankyrin repeat region in tankyrase has been shown to be responsible for the interaction with TRF1. Tankyrase has been shown to poly ADP-ribosylate TRF1 *in vitro* and it has been suggested that the role of tankyrase *in vivo* is to ADP-ribosylate TRF1 causing dissociation of TRF1 from the telomere repeats and thus allowing telomerase to replicate the telomeres. Drugs that inhibit tankyrase activity then might be expected to inhibit the replication of telomeres and thus cause eventual senescence of dividing cell populations such as cancer cells or proliferating immune system cell as examples.

As tankyrase or tankyrase-related gene products might be attractive targets of drug design, there is a need in the art to identify additional molecules with related functions and/or structures. Such molecules might serve as specificity controls for tankyrase targeted drugs or may themselves be suitable targets for drug discovery programs.

In view of the above considerations, it is clear that existing knowledge is lacking with respect to cellular DNA repair mechanisms, signaling, and induction of cellular replication, mechanisms of tumorigenesis, and treatment of cancer disease states. Thus, there exists a need in the art for the identification of additional tankyrase-like molecules for use in determining the selectivity of therapeutics designed to modulate tankyrase function and as targets in their own right for therapeutic intervention in human diseases. The profiling of tankyrase inhibitors on additional tankyrase gene products may allow for the tankyrase-selective drugs, which could be beneficial for particular indications, the reduction of undesirable side effects, or the targeting of therapeutics to selected tissues. Other purposes and advantages of the invention will be readily apparent to the artisan having ordinary skill in the art.

SUMMARY OF THE INVENTION

It has now been discovered that these and other purposes can be achieved by the present invention, which, in one aspect, provides purified and isolated tankyrase2 polypeptides, preferably human tankyrase2 polypeptides. In particular the invention provides a purified and isolated tankyrase2 polypeptide comprising the amino acid sequence defined in SEQ ID NO:133 (designated "TANK2-LONG") or SEQ ID NO:135 (designated "TANK2-SHORT"). The invention also provides polynucleotides encoding the tankyrase2 polypeptides. For example, the polynucleotide may comprise the coding region of the nucleotide sequence defined in SEQ ID NO:132 or SEQ ID NO:134.

The invention further provides polynucleotides that are complements to TANK2-encoding polynucleotides, as well as polynucleotides that hybridize under moderately stringent hybridization conditions to the coding or non-coding strand of the tankyrase2 polynucleotides. In a preferred case, the polynucleotide hybridizes to the complement of the polynucleotide defined in SEQ ID NO:132 or SEQ ID NO:134 under stringent hybridization conditions, and encodes a protein that: (a) has poly(ADP) polymerase activity, (b) interacts with damaged DNA, or (c) binds to telomere repeat-binding factors and/or modulates their activity.

The polynucleotides may be DNA molecules or RNA molecules. Certain desirable polynucleotides of the invention, e.g., oligonucleotide probes, may further comprise a detectable label moiety.

In another aspect, the invention provides an expression construct, comprising a tankyrase2-encoding polynucleotide, as well as host cells transformed or transfected with the expression constructs. The polynucleotide can be operatively linked to a heterologous promoter.

In a further aspect, the invention provides a method for producing a tankyrase2 polypeptide in a host cell modified to express the tankyrase polypeptide, comprising the steps of:

a) growing the host cell under conditions appropriate for expression of the tankyrase2 polypeptide; and

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b) isolating the tankyrase2 polypeptide from the host cell or the medium in which the host cell is grown.

In yet another aspect, the invention provides antibodies that are immunoreactive with a tankyrase2 polypeptide. For example, the antibodies may be selected from the group consisting of monoclonal antibodies, polyclonal antibodies, single chain antibodies (scFv antibodies), chimeric antibodies, bifunctional/bispecific antibodies, humanized antibodies, human antibodies, CDR-grafted antibodies, Fab fragments, Fab' fragments, F(ab')₂ fragments, and Fv fragments. Also provided are cell lines that produce such antibodies. There are also provided anti-idiotypic antibodies that are immunoreactive with tankyrase2-specific antibodies.

In still another aspect, the invention provides a method for identifying a binding partner of a tankyrase2 polypeptide, comprising:

- a) contacting the tankyrase2 polypeptide with a test compound under conditions that permit binding of the tankyrase2 polypeptide and the test compound;
- b) detecting binding of the test compound and the tankyrase2 polypeptide; and
- c) identifying the test compound as a binding partner of the tankyrase2 polypeptide.

For example, the method can be used to identify binding partners that selectively or specifically modulate, i.e., inhibit or enhance, a biological activity of the tankyrase2 polypeptide.

Also provided in another aspect is a method for identifying a binding partner of a tankyrase2 polynucleotide, comprising:

- a) contacting the tankyrase2 polynucleotide with a test compound under conditions that permit binding of the tankyrase2 polynucleotide and the test compound;
- b) detecting binding of the test compound and the tankyrase2 polynucleotide; and
- c) identifying the test compound as a binding partner of the tankyrase2 polynucleotide.

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The method may be used to identify binding partners that selectively or specifically modulate, i.e., inhibit or enhance, expression of the tankyrase2 polypeptide.

There is also provided by the invention a method of treating a human or animal subject having a medical condition mediated by poly(ADP-ribose) polymerase activity, comprising administering to the subject a tankyrase2 inhibitory compound in an amount effective for inhibiting tankyrase2 in the subject. In another aspect, the invention provides a method of treating a human or animal subject having a medical condition mediated by poly(ADP-ribose) polymerase activity, comprising administering to the subject a compound that inhibits tankyrase2 expression or activity in an amount effective for inhibiting poly(ADP-ribose) polymerase activity in the subject. The method is of particular interest in treating medical conditions associated with growth of neoplastic tissue. For example, the method can be used to treat cancers such as carcinomas, sarcomas, leukemias, and lymphomas. More particularly, the method may be used to treat cancers selected from the group consisting of ACTH-producing tumor, acute lymphocytic leukemia, acute nonlymphocytic leukemia, cancer of the adrenal cortex, bladder cancer, brain cancer, breast cancer, cervical cancer, chronic lymphocytic leukemia, chronic myelocytic leukemia, colorectal cancer, cutaneous T-cell lymphoma, endometrial cancer, esophageal cancer, Ewing's sarcoma, gallbladder cancer, hairy cell leukemia, head and neck cancer, Hodgkin's lymphoma, Kaposi's sarcoma, kidney cancer, liver cancer, lung cancer (small and non-small cell), malignant peritoneal effusion, malignant pleural effusion, melanoma, mesothelioma, multiple myeloma, neuroblastoma, glioma, non-Hodgkin's lymphoma, osteosarcoma, ovarian cancer, ovarian (germ cell) cancer, pancreatic cancer, penile cancer, prostate cancer, retinoblastoma, skin cancer, soft tissue sarcoma, squamous cell carcinomas, stomach cancer, testicular cancer, thyroid cancer, trophoblastic neoplasms, uterine cancer, vaginal cancer, cancer of the vulva, and Wilm's tumor.

These and other features and advantages of the present invention will be appreciated from the detailed description and examples that are set forth herein. The detailed description and examples are provided to enhance the understanding of the invention, but are not intended to limit the scope of the invention.

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DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention relates generally to a previously uncharacterized nucleic acid encoding a novel human protein designated "tankyrase2" (hereinafter also referred to as "TANK2"). As illustrated herein tankyrase2 is distinct from known tankyrase proteins and other proteins sharing poly(ADP-ribose) polymerase activity. The present invention is based on the discovery of novel gene encoding the tankyrase2 protein, and nucleic acid sequences, oligonucleotides, fragments, and antisense molecules thereof.

The nucleotide sequence information provided by the invention makes possible large-scale expression of the encoded TANK2 polypeptide by techniques well known and routinely practiced in the art. The invention also permits identification and isolation of polynucleotides encoding related TANK2 polypeptides by well-known techniques including Southern (DNA) and/or northern (mRNA) hybridization, and amplification techniques such as polymerase chain reaction (PCR), ligase chain reaction (LCR), and the like. Examples of related polynucleotides include human and non-human tank2 genomic sequences, including allelic variants, as well as polynucleotides encoding polypeptides homologous to TANK2 and structurally related polypeptides sharing one or more biological, immunological, and/or physical properties of TANK2.

The invention includes both naturally occurring and non-naturally occurring tankyrase2 polynucleotides and polypeptide products thereof. Naturally occurring tankyrase2 products include distinct polynucleotide and polypeptide tankyrase2 species as they occur in humans. However, the invention includes other human tankyrase2 polynucleotide and polypeptide species defined through the analysis of sequence homology. The invention further comprises corresponding homologs of human TANK2 polypeptides and tank2 polynucleotides that are expressed in cells of other animal species, preferably mammalian homologs, and more preferably primate homologs. Within each tankyrase2 species, the invention further provides splice variants, which are encoded by the same genomic DNA but arise from distinct mRNA transcripts. Non-naturally occurring tankyrase2 products include variants of the naturally occurring tankyrase2 products such as polynucleotide and polypeptide

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analogs (i.e., wherein one or more nucleotides or amino acids are added, substituted, or deleted). Non-naturally-occurring TANK2 polypeptide products also include TANK2 products that have been covalently modified, e.g., water-soluble polymer modifications, glycosylation variants, and the like.

5 The tankyrase2 polypeptides and the nucleic acids that encode the polypeptides provide a basis for diagnostic methods for the precise and accurate detection and/or quantitation of TANK2 expression and medical conditions associated with excessive or insufficient TANK2 activity. Furthermore, the nucleotide sequences disclosed herein may be used in the detection of aberrations, such as
10 mutations and deletions, in the gene encoding TANK2. For example, the nucleotide sequences disclosed herein may be used to identify and isolate a genomic sequence for tank2. PCR primers can be designed from various portions of the introns and exons of a genomic tank2 nucleic acid sequence that will allow detection of aberrations in the genomic sequence.

15 The invention further provides methods of using TANK2 and genetically engineered host cells that express recombinant TANK2 to evaluate and screen for modulators of the poly(ADP-ribose) polymerase activity of the enzyme. Such screening methods may be used for the identification of allosteric agonists and antagonists of TANK2 activity as well as for the identification of direct (e.g.,
20 competitive inhibitors) of such activity. TANK2 protein antagonists and inhibitors, such as anti-TANK2 antibodies and tank2 antisense molecules, will provide the basis for pharmaceutical compositions for the treatment and amelioration of symptoms associated with excessive poly(ADP-ribose) polymerase activity. Agonists of TANK2 will provide the basis of the treatment and amelioration of symptoms associated with
25 insufficient poly(ADP-ribose) polymerase activity.

Tankyrase2 Polynucleotides

30 The present invention provides, *inter alia*, novel purified and isolated polynucleotides encoding human TANK2 polypeptides. The polynucleotides of the invention include DNA sequences and RNA transcripts, both sense and complementary antisense strands, and splice variants thereof. DNA sequences of the

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invention include, without limitation, cDNA and genomic sequences. As used herein, lower case "tank2" refers to a tankyrase2 nucleic acid sequence whereas upper case "TANK2" refers to a tankyrase2 amino acid sequence.

"Nucleic acid" as used herein refers to an oligonucleotide or polynucleotide sequence, and fragments or portions thereof, and to DNA or RNA of genomic or synthetic origin, which may be double-stranded or single-stranded, whether representing the sense or antisense strand. An exemplary double-stranded polynucleotide according to the invention can have a first strand (i.e., a coding strand) having a sequence encoding a TANK2 polypeptide, along with a second strand (i.e., a "complementary" or "non-coding" strand) having a sequence deducible from the first strand according to the Watson-Crick base-pairing rules for DNA. Double-stranded or "duplex" structures may be DNA:DNA, DNA:RNA, or RNA:RNA nucleic acids. A preferred double-stranded polynucleotide is a cDNA comprising the coding region of a nucleotide sequence defined by SEQ ID NO:132 or SEQ ID NO:134. An exemplary single-stranded polynucleotide according to the invention is a messenger RNA (mRNA) encoding a TANK2 polypeptide. Another exemplary single-stranded polynucleotide is an oligonucleotide probe or primer that hybridizes to the coding or non-coding strand of a polynucleotide selected from among the sequences defined by SEQ ID NO:132, and SEQ ID NO:134. Other alternative nucleic acid structures, e.g., triplex structures, are also contemplated.

Genomic DNA of the invention comprises the protein-coding region for a TANK2 polypeptide and includes allelic variants of the preferred polynucleotides of the invention, such as single nucleotide polymorphisms. Genomic DNA of the invention is distinguishable from genomic DNAs encoding polypeptides other than TANK2 in that it includes the TANK2-coding region found in tank2 cDNA of the invention. Genomic DNA can be transcribed into RNA, and the resulting RNA transcript may undergo one or more splicing events wherein one or more introns (i.e., non-coding regions) of the transcript are removed, or "spliced out." RNA transcripts that can be spliced by alternative mechanisms and therefore be subjected to removal of different non-coding RNA sequences but still encode a TANK2 polypeptide, are referred to in the art as "splice variants," and are embraced by the invention. Splice

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variants comprehended by the invention, therefore, are encoded by the same DNA sequences but give rise to different amino acid sequences. Such splice variants can comprise regions in which the reading frame is shifted, wherein a downstream portion of the RNA sequence is translated differently, to yield different amino acid sequences in the resulting polypeptides. Allelic variants are known in the art to be modified forms of the wild-type (predominant) gene sequence. Such modifications result from recombination during chromosomal segregation or exposure to conditions that give rise to genetic mutation. Allelic variants, like wild-type genes, are naturally occurring sequences, as opposed to non-naturally occurring variants, which arise from *in vitro* manipulation.

The invention also comprehends cDNA, which is obtained through reverse transcription of an RNA polynucleotide encoding TANK2 followed by second strand synthesis of a complementary strand to provide a double stranded DNA. For example, the invention provides a cDNA sequence that encodes a polypeptide having an amino acid sequence selected from among the sequences defined by SEQ ID NO:133 and SEQ ID NO:135. In a preferred embodiment, the invention provides polynucleotides comprising the coding region of a nucleotide sequence selected from among the sequences defined by SEQ ID NO:132 and SEQ ID NO:134.

As noted, highly preferred nucleic acid sequences according to the invention are defined by SEQ ID NO:132 or SEQ ID NO:134. However, because the genetic code is redundant or "degenerate" in its information-encoding properties, different nucleotide sequences may encode the same polypeptide sequence. Accordingly, the invention comprises the alternative (degenerate) nucleotide sequences that encode TANK2 polypeptides of the invention and functional equivalents thereof. For example, the invention includes polynucleotides comprising nucleotide sequences that are substantially homologous to the TANK2-encoding regions of the nucleotide sequences set forth in SEQ ID NO:132 or SEQ ID NO:134. More particularly, the invention includes polynucleotides whose corresponding nucleotide sequences have at least 90%, preferably at least 95%, more preferably at least 98%, and still more preferably at least 99% identity with a nucleotide sequence defined in SEQ ID NO:132 or SEQ ID NO:134.

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Variant polynucleotides of the invention further include fragments of the tank2 nucleotide sequences defined in SEQ ID NO:132 and SEQ ID NO:134, and homologs thereof. The disclosure of full-length polynucleotides encoding TANK2 polypeptides makes readily available to the person having ordinary skill in the art every possible
5 fragment of the full-length polynucleotides. Preferably, fragment polynucleotides of the invention comprise sequences unique to the TANK2-coding nucleotide sequence, and therefore hybridize under highly stringent or moderately stringent conditions only (i.e., specifically) to polynucleotides encoding TANK2 or fragments thereof containing the unique sequence. Polynucleotide fragments of genomic sequences of
10 the invention comprise not only sequences unique to the coding region, but also include fragments of the full-length sequence derived from introns, regulatory regions, and/or other untranslated sequences. Sequences unique to polynucleotides of the invention are recognizable through sequence comparison to other known polynucleotides, and can be identified through use of computer software routinely
15 used in the art, e.g., alignment programs available in public sequence databases.

The invention also provides fragment polynucleotides that are conserved in one or more polynucleotides encoding members of the TANK2 family of polypeptides. Such fragments include sequences characteristic of the family of TANK2 polypeptides, referred to as "signature" sequences. The conserved signature
20 sequences are readily discernable following simple sequence comparison of polynucleotides encoding members of the TANK2 family. Polynucleotide fragments of the invention can be labeled in a manner that permits their detection, including radioactive and non-radioactive labeling.

Hybridization can be defined to include the process of forming partially or
25 completely double-stranded nucleic acid molecules through sequence-specific association of complementary single-stranded nucleic molecules. The invention, therefore, further encompasses the use of nucleic acid species that hybridize to the coding or non-coding strands of a polynucleotide that encodes a TANK2 protein. Preferred hybridizing species hybridize to the coding or non-coding strand of the
30 nucleotide sequence defined by SEQ ID NO:132 or SEQ ID NO:134. Also encompassed are species that would hybridize to a TANK2-encoding polynucleotide

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but for the redundancy of the genetic code, i.e., polynucleotides that encode the same amino acid sequence but rely on different codon usage.

Hybridizing species include, for example, nucleic acid hybridization or amplification probes (oligonucleotides) that are capable of detecting nucleotide sequences (e.g., genomic sequences) encoding TANK2 or closely related molecules, such as alleles. The specificity of the probe, i.e., whether it is derived from a highly conserved, conserved, or non-conserved region or domain, and the stringency of the hybridization or amplification conditions (high, intermediate, or low) will determine whether the probe identifies only naturally occurring tank2, or related sequences.

Probes for the detection of related nucleotide sequences are selected from conserved or highly conserved regions of tank2 family members and such probes may be used in a pool of degenerate probes. For the detection of identical nucleotide sequences, or where maximum specificity is desired, oligonucleotide probes are selected from the non-conserved nucleotide regions or unique regions of tank2 polynucleotides. As used herein, the term "non-conserved nucleotide region" refers to a nucleotide region that is unique to tank2 disclosed herein and does not occur in related tank2 family members.

Specificity of hybridization is typically characterized in terms of the degree of stringency of the conditions under which the hybridization is performed. The degree of stringency of hybridization conditions can refer to the melting temperature (T_m) of the nucleic acid binding complex [see, e.g., Berger and Kimmel, "Guide to Molecular Cloning Techniques," *Methods in Enzymology*, Vol. 152, Academic Press, San Diego, CA (1987)]. "Maximal stringency" typically occurs at about $T_m - 5^\circ\text{C}$ (5°C below the T_m of the probe); "high stringency" at about 5°C to 10°C below T_m ; "intermediate stringency" at about 10°C to 20°C below T_m ; and "low stringency" at about 20°C to 25°C below T_m .

Alternatively, the stringency of hybridization can refer to the physicochemical conditions employed in the procedure. To illustrate, exemplary moderately stringent hybridization conditions are: hybridization in 3X saline sodium citrate (SSC), 0.1% sarkosyl, and 20 mM sodium phosphate, pH 6.8, at 65°C ; and washing in 2X SSC with 0.1% sodium dodecyl sulfate (SDS), at 65°C . Exemplary highly stringent

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hybridization conditions are: hybridization in 50% formamide, 5X SSC, at 42°C overnight, and washing in 0.5X SSC and 0.1% SDS, at 50°C. It is understood in the art that conditions of equivalent stringency can be achieved through variation of temperature and buffer, or salt concentration as described Ausubel et al. (Eds.),

5 *Current Protocols in Molecular Biology*, John Wiley & Sons (1994), at pp. 6.0.3-6.4.10. Modifications in hybridization conditions can be determined empirically or calculated precisely based on the length of the oligonucleotide probe and the percentage of guanosine/cytosine (GC) base pairing of the probe. The hybridization conditions can be calculated as described in Sambrook et al., (Eds.), *Molecular*
10 *Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press: Cold Spring Harbor, New York (1989), pp. 9.47-9.51.

 The artisan will appreciate that hybridization under more stringent conditions enables the identification of species having a higher degree of homology or sequence identity with the target sequence. By contrast, hybridization under less stringent
15 conditions enables identification of species having a lesser but still significant degree of homology or sequence identity with the target sequence. Therefore, also included within the scope of the present invention are nucleic acid species that are capable of hybridizing to the nucleotide sequence of SEQ ID NO:132 or SEQ ID NO:134 under
— conditions of intermediate (moderate) to maximal stringency. Preferably, the
20 hybridizing species hybridize to the coding or non-coding strands of a polynucleotide defined by SEQ ID NO:132 or SEQ ID NO:134 under highly stringent conditions.

 The polynucleotides of the invention encompass oligonucleotides (i.e., nucleic acid oligomers typically about 10 to 60 nucleotides in length) that hybridize to either the coding or the non-coding strands of a nucleic acid encoding a TANK2 amino acid
25 sequence. In particular, the invention comprises oligonucleotides that hybridize to the coding or non-coding strand of a polynucleotide defined by SEQ ID NO:132 or SEQ ID NO:134. The length of the oligonucleotide is not critical, as long as it is capable of hybridizing to the target nucleic acid molecule. However, longer nucleic acid molecules are more difficult to prepare and require longer hybridization times.
30 Therefore, the oligonucleotide should not be longer than necessary. Accordingly, the oligonucleotide should contain at least 10 nucleotides, preferably at least 15

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nucleotides, and more preferably at least 20 nucleotides. Normally, the oligonucleotide will not contain more than 60 nucleotides, preferably not more than 30 nucleotides, and more preferably not more than 25 nucleotides. Such oligonucleotides may be used as described herein as primers for DNA synthesis (e.g., as primers in PCR; “amplimers”), as probes for detecting the presence of target DNA in a sample (e.g., northern or Southern blots and *in situ* hybridization), as therapeutic agents (e.g., in antisense therapy), or for other purposes. Oligonucleotides may be single- or double-stranded, with the double-stranded forms having one or both ends blunt or stepped.

The oligonucleotides may be obtained or derived by known methods from natural sources. Alternatively, the oligonucleotides may be produced synthetically according to methods known in the art. Such methods include, for example, cloning and restriction of appropriate sequences or direct chemical synthesis by any suitable method. Various chemical methods for making oligonucleotides are known in the art, including the phosphotriester method, the phosphodiester method; the diethylphosphoramidite method; the solid support method, and the H-phosphonate method [for reviews, see Caruthers, *Science* 230:281-5 (1985); Caruthers et al., *Methods Enzymol* 211:3-20 (1992)]. Typically, preparation of oligonucleotides is carried out by automated phosphoramidite synthesis on polymer support. Nucleic acid molecules consisting of 100 or more nucleotides may also be produced by such methods.

The tank2 polynucleotides of the invention include variants, which are polynucleotides that encode hAPRP2 or a functional equivalent thereof, and which can include deletions, insertions, or substitutions of nucleotide residues. As used herein a “deletion” is a change in a nucleotide or amino acid sequence in which one or more nucleotides or amino acid residues, respectively, are absent. As used herein an “insertion” or “addition” is a change in a nucleotide or amino acid sequence that results in the addition of one or more nucleotides or amino acid residues, respectively. As used herein a “substitution” is a change in a nucleotide or amino acid sequence in which one or more nucleotides or amino acids are replaced by different nucleotides or amino acids, respectively.

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Polynucleotide variants also included within the scope of the present invention are alleles or alternative naturally occurring forms of tank2. Alleles result from naturally occurring mutations, i.e., deletions, insertions or substitutions, in the genomic nucleotide sequence, which may or may not alter the structure or function or the expressed polypeptides. Each of these types of mutational changes may occur alone, or in combination with the others, one or more times in a given allelic sequence. Single nucleotide polymorphisms (SNPs) may occur, in which a single base mutation may define an altered polypeptide, which in turn may be associated with an overt phenotypic difference. Of course, SNPs may be silent, as they may not change the encoded polypeptide, or any change they do encode may have no effect on phenotype.

The invention further embraces natural homologs of the human tankyrase2 DNA that occur in other animal species, such as other mammal species. Mammalian homologs include, for example, homologs in mouse, rat, guinea pig, and the like, and more preferably homologs in other primate species. Such species homologs, in general, share significant homology at the nucleotide level within the protein-coding regions. Thus, the invention encompasses polynucleotides that share at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% nucleotide identity with the protein-coding region of a polynucleotide encoding a human TANK2 polypeptide, e.g., a polynucleotide defined by SEQ ID NO:132 or SEQ ID NO:134. Percent sequence "homology" with respect to polynucleotides of the invention can be defined as the percentage of nucleotide bases in a candidate sequence that are identical to nucleotides in the TANK2-encoding sequence after aligning the sequences and introducing gaps, if necessary, to achieve maximum percent sequence identity. Computer software is available (from commercial and public domain sources) for calculating percent identity in an automated fashion (e.g., FASTA).

The invention includes polynucleotides that have been engineered to selectively modify the cloning, processing, and/or expression of the TANK2 gene product. Mutations may be introduced using techniques well known in the art, e.g., site-directed mutagenesis to insert new restriction sites, to alter glycosylation patterns,

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or to change codon preferences inherent in the use of certain expression systems, while simultaneously maintaining control of the amino acid sequence of the expressed polypeptide product. For example, codons preferred by a particular prokaryotic or eukaryotic host cell can be selected ("codon optimization") to increase the rate of TANK2 expression or to produce recombinant RNA transcripts having desirable properties, such as longer half-lives.

The tank2 polynucleotides can be synthesized, wholly or partly, using chemical methods well known in the art. "Chemically synthesized," as used herein and is understood in the art, refers to purely chemical, as opposed to enzymatic, methods for producing polynucleotides. "Wholly" chemically synthesized DNA sequences are therefore produced entirely by chemical means; "partly" chemically synthesized DNAs embrace those wherein only portions of the resulting DNA were produced by chemical means.

DNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences of the 5' and/or 3' ends of the molecule or the use of phosphorothioate or 2' O-methyl rather than phosphodiester linkages within the backbone of the molecule.

The invention also provides TANK2 peptide nucleic acid (PNA) molecules. These TANK2 PNAs are informational molecules that have a neutral "peptide-like" backbone with nucleobases that allow the molecules to hybridize to complementary TANK2-encoding DNA or RNA with higher affinity and specificity than corresponding oligonucleotides (PerSeptive Biosystems).

Polypeptide Expression Systems

Knowledge of TANK2-encoding DNA sequences enables the artisan to modify cells to permit or increase expression of TANK2. Accordingly, host cells are provided, including prokaryotic or eukaryotic cells, either stably or transiently modified by introduction of a polynucleotide of the invention to permit expression of the encoded TANK2 polypeptide. Autonomously replicating recombinant expression constructs such as plasmid and viral DNA vectors incorporating TANK2-encoding sequences are also provided.

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Expression constructs are also provided comprising TANK2-encoding polynucleotides operatively linked to an endogenous or exogenous expression control DNA sequence and a transcription terminator. Expression control DNA sequences include promoters, enhancers, and operators, and are generally selected based on the expression systems in which the expression construct is to be used. Preferred promoter and enhancer sequences are generally selected for the ability to increase gene expression, while operator sequences are generally selected for the ability to regulate gene expression. Preferred constructs of the invention also include sequences necessary for replication in a host cell. Expression constructs are preferably used for production of an encoded TANK2 polypeptide, but may also be used to amplify the construct itself.

Polynucleotides of the invention may be introduced into the host cell as part of a circular plasmid, or as linear DNA comprising an isolated protein coding region or a viral vector. Methods for introducing DNA in to a host cell include transformation, transfection, electroporation, nuclear injection, or fusion with carriers such as liposomes, micelles, ghost cells, and protoplasts. Expression systems of the invention include, for example, bacteria, yeast, fungal, plant, insect, invertebrate, amphibian, and mammalian cell systems. Some suitable prokaryotic host cells include, for example, *E. coli* strains SG-936, HB 101, W3110, X1776, X2282, DH1, and MRC1, *Pseudomonas* sp., *Bacillus* sp. such as *B. subtilis*, and *Streptomyces* sp. Suitable eukaryotic host cells include yeasts, such as *Saccharomyces cerevisiae*, *S. pombe*, *Pichia pastoris* and other fungi, insect cells such as sf9 or sf21 cells (*Spodoptera frugiperda*), animal cells such as Chinese hamster ovary (CHO) cells, human cells such as JY, 293, and NIH3T3 cells, and plant cells such as *Arabidopsis thaliana* cells. The tank2 nucleotide sequence, or any portion of it, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes *in vitro* by addition of labeled nucleotides and an appropriate RNA polymerase such as T7, T3, or SP6.

The type of host cell, the form of the expressed TANK2 product, the conditions of growth, etc., can be selected by the skilled artisan according to known

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criteria. Use of mammalian host cells is expected to provide for such post-translational modifications (e.g., glycosylation, truncation, lipidation, and phosphorylation) as may be needed to confer optimal biological activity on recombinant expression products of the invention. Glycosylated and non-glycosylated forms of TANK2 polypeptides are embraced. The protein produced by a recombinant cell may be secreted or may be contained intracellularly, depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing tank2 can be designed with signal sequences that direct secretion of TANK2 through a particular prokaryotic or eukaryotic cell membrane.

Expression constructs may include sequences that facilitate, and preferably promote, homologous recombination in a host cell. This can be accomplished by replacing all or part of the naturally occurring tank2 promoter with all or part of a heterologous promoter so that the cells express TANK2 at higher levels. The heterologous promoter should be inserted so that it is operatively linked to TANK2-encoding sequences. See, for example, PCT International Publication Nos. WO 94/12650, WO 92/20808, and WO 91/09955.

Host cells of the invention are useful in methods for large-scale production of TANK2 polypeptide products. For example, host cells of the invention are a valuable source of immunogen for development of antibodies that are immunoreactive with TANK2 polypeptides. As another example, recombinant TANK2 can be produced and isolate from host cells for use in *in vitro* binding assays such as drug screening assays. In such methods, the host cells are grown in a suitable culture medium and the desired polypeptide product is isolated from the cells or from the medium in which the cells are grown.

The polypeptide product can be isolated by purification methods known in the art, such as conventional chromatographic methods including immunoaffinity chromatography, receptor affinity chromatography, hydrophobic interaction chromatography, lectin affinity chromatography, size exclusion filtration, cation or anion exchange chromatography, high performance liquid chromatography (HPLC), reverse phase HPLC, and the like.

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Still other methods of purification include those in which the desired protein is expressed and purified as a fusion protein in which the TANK2 polypeptide is ligated to a heterologous amino acid sequence. Suitable heterologous sequences can include a specific tag, label, or chelating moiety that is recognized by a specific binding partner or agent. For example, for screening of peptide libraries for modulators of TANK2 activity, it is possible to express a TANK2 protein fused to a selected heterologous protein selected to be specifically identifiable using a probe antibody. A fusion protein may also be engineered to contain a cleavage site (e.g., a factor XA or enterokinase sensitive sequence) located between the TANK2 sequence and the heterologous protein sequence, to permit the TANK2 protein to be cleaved from the heterologous protein and subsequently purified. Cleavage of the fusion component may produce a form of the desired protein having additional amino acid residues resulting from the cleavage process.

Exemplary heterologous peptide domains include metal-chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals [Porath, *Protein Expr Purif* 3:263-81 (1992)], and protein A domains that allow purification on immobilized immunoglobulin. Another useful system is the divalent cation-binding domain and antibodies specific thereto used in the peptide extension/immunoaffinity purification system described in US Patents Nos. 4,703,004; 4,782,137; 4,851,431; and 5,011,912. This system is commercially available as the FLAG® system from Immunex Corp. (Seattle WA). Another suitable heterologous fusion partner is glutathione S-transferase (GST), which can be affinity purified using immobilized glutathione. Other useful fusion partners include immunoglobulins and fragments thereof, e.g., Fc fragments.

Identification of host cells expressing recombinant TANK2 may be crucial to identifying appropriate expression systems. Accordingly, expression constructs of the invention may also include sequences encoding one or more selectable markers that permit identification of host cells bearing the construct in operative condition. It is also contemplated that, in addition to the insertion of heterologous promoter DNA, amplifiable marker DNA (e.g., *ada*, *dhfr*, and the multifunctional CAD gene that encodes carbamyl phosphate synthase, aspartate transcarbamylase, and

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dihydroorotase) and/or intron DNA may be inserted along with the heterologous promoter DNA. If linked to the TANK2-encoding sequence, amplification of the marker DNA by standard selection methods results in co-amplification of the TANK2-encoding sequences in the cells. Detection of expression of the marker gene in response to induction or selection usually indicates expression of TANK2 as well. Alternatively, if the tank2 polynucleotide is inserted within a marker gene sequence, recombinant cells containing tank2 can be identified by the absence of marker gene function.

Host cells that contain the coding sequence for TANK2 and express TANK2 may also be identified by a variety of other procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridization and protein bioassay or immunoassay techniques that include membrane-based, solution-based, or chip-based technologies for the detection and/or quantification of the nucleic acid or protein.

The presence of the tank2 polynucleotide sequence can be detected by DNA-DNA or DNA-RNA hybridization or amplification using fragments of a tank2 polynucleotide, e.g., fragments of the sequences set forth in SEQ ID NO:132 or SEQ ID NO:134, as probes. Nucleic acid amplification based assays involve the use of oligonucleotides based on the tank2 sequence to detect transformants containing tank2 DNA or RNA. Labeled hybridization or PCR probes for detecting tank2 polynucleotide sequences can be made by various methods, including oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. In an embodiment of the present invention, TANK2 or a variant thereof and/or a host cell line that expresses the TANK2 or variant thereof may be used to screen for antibodies, peptides, or other molecules, such as organic or inorganic molecules, that act as modulators of a biological or immunological activity of TANK2. For example, anti-TANK2 antibodies capable of neutralizing the polymerase or DNA-binding activity of TANK2 may be used to inhibit TANK2-mediated cell death. Alternatively, screening of peptide libraries or organic libraries made by combinatorial chemistry with recombinantly expressed TANK2 or variants thereof or cell lines expressing TANK2 or variants thereof may be useful for identification of therapeutic molecules

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that function by modulating a biological or immunological activity of TANK2. Synthetic compounds, natural products, and other sources of potentially biologically active materials can be screened in a number of ways deemed routine by those of skill in the art. For example, nucleotide sequences encoding the DNA-binding domain of TANK2 may be expressed in a host cell, which can be used for screening of allosteric modulators, either agonists or antagonists, of TANK2 activity. Alternatively, nucleotide sequences encoding the conserved catalytic domain of TANK2 can be expressed in host cells and used to screen for inhibitors of ADP-ribose polymerization.

TANK2 Polypeptides

The invention also provides purified and isolated mammalian TANK2 polypeptides. Exemplary TANK2 polypeptides have amino acid sequences defined in SEQ ID NO:133 or SEQ ID NO:135. TANK2 polypeptides of the invention may be isolated from natural cell sources or may be chemically synthesized, but are preferably produced by recombinant procedures involving host cells of the invention. TANK2 products of the invention may be full-length polypeptides, or variant polypeptide products such as fragments, truncates, deletion mutants, and other variants thereof that retain specific TANK2 biological activity. As used herein, "biologically active" refers to a TANK2 polypeptide having structural, regulatory or biochemical functions of the naturally occurring TANK2 protein. Specifically, a TANK2 protein of the present invention has the ability to bind DNA and to polymerize ADP-ribose subunits in response to DNA damage in a cell.

The protein and fragments of the present invention may be prepared by methods known in the art. Such methods include isolating the protein directly from cells, isolating or synthesizing DNA encoding the protein and using the DNA to produce recombinant protein, and synthesizing the protein chemically from individual amino acids.

The TANK2 polypeptides can be isolated from a biological sample, such as a solubilized cell fraction, by standard methods. Some suitable methods include precipitation and liquid chromatographic protocols such as ion exchange, hydrophobic

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interaction, and gel filtration [see, e.g., Deutscher (Ed.), *Methods Enzymol (Guide to Protein Chemistry*, Section VII) 182:309 (1990) and Scopes, *Protein Purification*, Springer-Verlag, New York (1987)]. Alternatively, purified material is obtained by separating the protein on preparative SDS-PAGE gels, slicing out the band of interest and electroeluting the protein from the polyacrylamide matrix by methods known in the art. The detergent SDS is removed from the protein by known methods, such as by dialysis or the use of a suitable column, such as the Extracti-Gel® column from Pierce Chemical Co. (Rockford, IL).

The TANK2 polypeptide of the invention may also be chemically synthesized, wholly or partly, by methods known in the art [see, e.g., Stuart and Young, *Solid Phase Peptide Synthesis*, 2d ed., Pierce Chemical Co. (1984)]. For example, peptides can be synthesized by solid phase techniques, cleaved from the resin, and purified by preparative HPLC [see, e.g., Roberge et al., *Science* 269:202-4 (1995)]. Automated synthesis may be accomplished, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Norwalk, CT) in accordance with the instructions provided by the manufacturer. The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (e.g., the Edman degradation procedure).

Recombinant TANK2 protein may be produced in and isolated from a host cell transformed with an expression vector containing a tank2 nucleotide sequence and grown in cell culture. As described herein, the host cells, either prokaryotic or eukaryotic, are either stably or transiently transfected (eukaryotic) or transformed (prokaryotic) with a TANK2-encoding polynucleotide of the invention in manner that permits directed expression of a TANK2 polypeptide. In such methods, the host cells are grown in a suitable culture medium and the desired polypeptide products are isolated from the cells or from the medium in which the cells are grown. Isolation of the polypeptides can be accomplished by, for example, immunoaffinity purification. The use of transformed host cells is preferred for large-scale production of TANK2 polypeptides.

The invention includes polypeptides comprising amino acid sequences that are substantially homologous to the sequences of TANK2 polypeptides described herein. For example, the invention includes polypeptides whose corresponding amino acid

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sequences have at least 90%, preferably at least 95%, more preferably at least 98%, and still more preferably at least 99% identity with the polypeptide sequence defined in SEQ ID NO:133 or SEQ ID NO:135.

Percent sequence "identity" with respect to a preferred polypeptide of the invention can be defined as the percentage of amino acid residues in a candidate sequence that are identical to amino acid residues in the reference TANK2 sequence after aligning the sequences and introducing gaps, if necessary, to achieve maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity.

Percent sequence "homology" with respect to a preferred polypeptide of the invention can be defined as the percentage of amino acid residues in a candidate sequence that are identical to amino acid residues in the reference TANK2 sequence after aligning the sequences and introducing gaps, if necessary, to achieve maximum percent sequence identity, and also considering any conservative substitutions as part of the sequence identity.

Determinations of whether two amino acid sequences are substantially homologous can also be based on FASTA searches [Pearson et al., *Proc Natl Acad Sci USA* 85:2444-8 (1988)]. Alternatively, percent homology is calculated as the percentage of amino acid residues in the smaller of the two sequences that align with identical amino acid residues in the sequence being compared, when four gaps in a length of 100 amino acids may be introduced to maximize alignment [see Dayhoff, in *Atlas of Protein Sequence and Structure*, Vol. 5, National Biochemical Research Foundation, Washington, D.C. (1972), at p. 124].

A polypeptide may be considered homologous to a TANK2 polypeptide of the invention if polynucleotides encoding the two polypeptides hybridize with one another. A higher degree of homology is shown if the hybridization occurs under hybridization conditions of greater stringency. Control of hybridization conditions and the relationships between hybridization conditions and degree of homology are understood by those skilled in the art [see, e.g., Sambrook et al., *supra*]. Thus, a

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homologous polypeptide may be a polypeptide that is encoded by a polynucleotide that hybridizes with a polynucleotide encoding a polypeptide of the invention under hybridization conditions having a specified degree of stringency.

5 It may be desirable that such structurally homologous polypeptides will also exhibit functional homology, insofar as the homologous polypeptide has substantially the same function as the polypeptide of the invention. For example, structurally homologous polypeptides may be considered functionally homologous if they exhibit similar binding of a ligand, or similar immune reactivity, etc.

10 However, it is known that two polypeptides or two polynucleotides may be considered to be substantially homologous in structure, and yet differ substantially in function. For example, single nucleotide polymorphisms (SNPs) among alleles may be expressed as polypeptides having substantial differences in function along one or more measurable parameters such as antibody- or ligand-binding affinity or enzymatic substrate specificity, and the like. Other structural differences, such as substitutions, 15 deletions, splicing variants, and the like, may affect the function of otherwise structurally identical or homologous polypeptides.

The TANK2 polypeptides of the invention include functional derivatives of a TANK2 polypeptides defined in SEQ ID NO:133 or SEQ ID NO:135. Such functional derivatives include polypeptide products that possesses a structural feature 20 or a biological activity that is substantially similar to a structural feature or a biological activity of the TANK2 protein. Accordingly, functional derivatives include variants, fragments, and chemical derivatives of the parent TANK2 protein.

As used herein "variant" refers to a molecule substantially similar in structure and function to either the entire TANK2 molecule, or to a fragment thereof. A 25 molecule is said to be "substantially similar" to another, if both molecules have substantially similar structures or if both molecules possess a similar biological activity. Thus, provided that two molecules possess a similar activity, they are considered variants, as that term is used herein, even if one of the molecules possesses a structure not found in the other molecule, or if the sequence of amino acid residues 30 is not identical.

Among the variant polypeptides provided under the invention are variants that

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comprise one or more changes in the amino acid sequence of the TANK2 polypeptide. Such sequence-based changes include deletions, substitutions, or insertions in the TANK2 sequence, as well as combinations thereof.

Deletion variants of the TANK2 polypeptides are polypeptides in which at least one amino acid residue of the sequence is removed. Deletions can be effected at one or both termini of the protein, or with removal of one or more residues within the TANK2 amino acid sequence. Deletion variants include, for example, all incomplete fragments of the TANK2 polypeptides of the invention. As used herein "fragment" refers to any polypeptide subset of the TANK2 protein.

Fragments of TANK2 that exhibit a biological activity characteristic of TANK2 and that are soluble (i.e., not membrane bound) are desirable. A soluble fragment is preferably generated by deleting any membrane-spanning region(s) of the parent molecule or by deleting or substituting hydrophilic amino acid residues for hydrophobic residues. Identification of such residues is well known in the art.

Substitution variants are provided, including polypeptides in which at least one amino acid residue of a TANK2 polypeptide is replaced by an alternative residue. Any substitution can be made, with conservative substitutions being preferred. Directed amino acid substitutions may be made based on well defined physicochemical parameters of the canonical and other amino acids (e.g., the size, shape, polarity, charge, hydrogen-bonding capacity, solubility, chemical reactivity, hydrophobicity, hydrophilicity, or the amphipathic character of the residues.) as well as their contribution to secondary and tertiary protein structure. Substitution variants can include polypeptides comprising one or more conservative amino acid substitutions, i.e., a substitution of one amino acid by another having similar physicochemical character as desired. To illustrate, the canonical amino acids can be grouped according to the following categories:

Aliphatic Side Chains	Gly, Ala; Val, Leu, Ile
Aromatic Side Chains	Phe, Tyr, Trp
Aliphatic Hydroxyl Side Chains	Ser, Thr
Basic Side Chains	Lys, Arg, His
Acidic Side Chains	Asp, Glu
Amide Side Chains	Asn, Gln
Sulfur-Containing Side Chains	Cys, Met
Secondary Amino Group	Pro

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Substitutions are preferably made in accordance with the following Table 1 when it is desired to controllably define the characteristics of the TANK2 molecule.

TABLE 1

	Original Residue	Exemplary Conservative Substitutions
5	Ala	gly; ser
	Arg	lys
	Asn	gln; his
10	Asp	glu
	Cys	ser
	Gln	asn
	Glu	asp
	Gly	ala; pro
15	His	asn; gln
	Ile	leu; val
	Leu	ile; val
	Lys	arg; gln; glu
	Met	leu; tyr; ile
20	Phe	met; leu; tyr
	Ser	thr
	Thr	ser
	Trp	tyr
	Tyr	trp; phe
25	Val	ile; leu

Substantial changes in functional or immunological identity are made by selecting substitutions that are more progressive than those in Table 1, i.e., selecting residues that differ more significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. The substitutions that are in general more progressive are those in which: (a) glycine and/or proline is substituted by another amino acid or is deleted or inserted; (b) a hydrophilic residue is substituted for a hydrophobic residue; (c) a cysteine residue is substituted for (or by) any other residue; (d) a residue having an electropositive side chain is substituted for (or by) a residue having an electronegative charge; or (e) a residue having a bulky side chain is substituted for (or

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by) one not having such a side chain. Most preferred are amino acid substitutions that affect the solubility of TANK2. These are most preferably generated by substituting hydrophilic for hydrophobic amino acids.

5 Substitution variants, however, can include non-canonical or non-naturally occurring amino acid residues substituted for amino acid residues in the principal sequence. Substitution variants include those polypeptides in which amino acid substitutions have been introduced by modification of polynucleotides encoding a TANK2 polypeptide.

10 Insertion variants are provided, in which at least one amino acid residue is present in addition to a TANK2 amino acid sequence. Insertions may be located at either or both termini of the polypeptide, or may be positioned within the TANK2 amino acid sequence. Insertional variants also include fusion proteins in which the amino or carboxy terminus of the TANK2 polypeptide is fused to another polypeptide. Examples of such fusion proteins include immunogenic polypeptides, proteins with
15 long circulating half-life (e.g., immunoglobulin constant regions), marker proteins (e.g., green fluorescent protein) and proteins or polypeptides that facilitate purification of the desired TANK2 polypeptide (e.g., FLAG® tags or polyhistidine sequences). Another example of a terminal insertion is a fusion of a signal sequence, whether heterologous or homologous to the host cell, to the N-terminus of the molecule to
20 facilitate the secretion of the derivative from recombinant hosts. Intrasequence insertions (i.e., insertions within a TANK2 molecule sequence) may range generally from about 1 to 10 residues, more preferably 1 to 5.

Polypeptide variants of the invention also include mature TANK2 products, i.e., TANK2 products wherein leader or signal sequences are removed, as well as
25 products having additional amino terminal residues. TANK2 products having an additional methionine residue at position -1 (Met⁻¹-TANK2) are contemplated, as are TANK2 products having additional methionine and lysine residues at positions -2 and -1, respectively (Met⁻²-Lys⁻¹-TANK2). Other such variants are particularly useful for recombinant protein production in bacterial host cells.

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The invention also encompasses TANK2 variants having additional amino acid residues resulting from use of specific expression systems. For example, use of commercially available vectors that express a desired polypeptide as a glutathione-S-transferase (GST) fusion product yields the desired polypeptide having an additional
5 glycine residue at position -1 (Gly⁻¹-TANK2) upon cleavage of the GST component from the desired polypeptide. Variants that result from expression in other vector systems are also contemplated.

The invention further provides TANK2 polypeptide products that are chemical derivatives of a TANK2 polypeptide defined in SEQ ID NO:133 or SEQ ID NO:135.
10 As used herein, the term "chemical derivative" refers to molecules that contain additional chemical moieties that are not normally a part of the naturally occurring molecule. Such moieties may impart desirable properties to the derivative molecule, such as increased solubility, absorption, biological half-life, etc. The moieties may alternatively decrease the toxicity of the derivative molecule, or eliminate or attenuate
15 any undesirable side effect of the derivative molecule. Thus, chemical derivatives of TANK2 polypeptides include polypeptides bearing modifications other than (or in addition to) insertion, deletion or substitution of amino acid residues. Preferably, the modifications are covalent in nature, and include, for example, chemical bonding with polymers, lipids, non-naturally occurring amino acids, and other organic and inorganic
20 moieties. Derivatives of the invention may be prepared to increase circulating half-life of a TANK2 polypeptide, or may be designed to improve targeting capacity for the polypeptide to desired cells, tissues, or organs.

For example, methods are known in the art for modifying a polypeptide to include one or more water-soluble polymer attachments such as polyethylene glycol,
25 polyoxyethylene glycol, or polypropylene glycol. Particularly preferred are TANK2 products that have been covalently modified with polyethylene glycol (PEG) subunits. Water-soluble polymers may be bonded at specific positions, for example at the amino terminus of the TANK2 products, or randomly attached to one or more side chains of the polypeptide. Additional derivatives include TANK2 species

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immobilized on a solid support, pin microparticle, or chromatographic resin, as well as TANK2 species modified to include one or more detectable labels, tags, chelating agents, and the like.

5 Derivatization with bifunctional agents can be used to cross-link TANK2 to a water-insoluble support matrix. Alternatively, reactive water-insoluble matrices such as cyanogen bromide-activated carbohydrates and reactive substrates may be employed for protein immobilization [see, e.g., US Patent Nos. 3,969,287; 3,691,016; 4,195,128; 4,247,642; 4,229,537; and 4,330,440.]

10 Expression of TANK2 variants can be expected to have utility in investigating a biological activity characteristic of a wild-type TANK2 polypeptide. TANK2 variants can be designed to retain all biological or immunological properties characteristic for TANK2, or to specifically disable one or more particular biological or immunological properties of TANK2. For example, fragments and truncates may be designed to delete a domain associated with a particular property, or substitutions and deletions may be designed to inactivate a property associated with a particular domain. Forced expression (overexpression) of such variants ("dominant negative" mutants) can be employed to study the function of the protein *in vivo* by observing the phenotype associated with the mutant.

20 Functional derivatives of TANK2 having up to about 100 residues may be conveniently prepared by *in vitro* synthesis. If desired, such fragments may be modified using methods known in the art by reacting targeted amino acid residues of the purified or crude protein with an organic derivatizing agent that is capable of reacting with selected side chains or terminal residues. The resulting covalent derivatives may be used to identify residues important for biological activity.

25 Functional derivatives of TANK2 having altered amino acid sequences can also be prepared by mutating the DNA encoding TANK2. Any combination of amino acid deletion, insertion, and substitution may be employed to generate the final

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construct, provided that the final construct possesses the desired activity. Obviously, the mutations that will be made in the DNA encoding the functional derivative must not place the sequence out of reading frame and preferably will not create complementary regions that could produce secondary mRNA structure [see EP Patent
5 Publication No. 75,444].

While the site for introducing a variation in the amino acid sequence is predetermined, the mutation per se need not be predetermined. For example, to optimize the performance of a mutation at a given site, random mutagenesis, such as linker scanning mutagenesis, may be conducted at a target codon or target region to
10 create a large number of derivative which could then be expressed and screened for the optimal combination of desired activity. Alternatively, site-directed mutagenesis or other well-known technique may be employed to make mutations at predetermined sites in a DNA known sequence.

The technique of site-directed mutagenesis is well known in the art [see, e.g.,
15 Sambrook et al., *supra*, and McPherson (Ed.), *Directed Mutagenesis: A Practical Approach*, IRL Press, Oxford (1991)]. Site-directed mutagenesis allows the production of TANK2 functional derivatives through use of specific oligonucleotide sequences that encode the DNA sequence of the desired mutation. Site-directed mutagenesis methods and materials are commercially available, e.g., the
20 QuikChange™ kit available from Stratagene (La Jolla, CA). One can selectively generate precise amino acid deletions, insertions, or substitutions using this method. Amino acid sequence deletions generally range from about 1 to 30 residues, more preferably 1 to 10 residues, and typically are contiguous. The most preferred deletions are those that are performed to generate catalytic fragments or DNA-binding
25 fragments.

Mutations designed to increase the affinity of TANK2 may be guided by the introduction of the amino acid residues that are present at homologous positions in other poly(ADP-ribose) polymerase proteins. Similarly, such mutant TANK2 molecules may be prepared that lack residues of a functional domain, e.g., the
30 catalytic domain, to create a dominant negative protein.

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It is difficult to predict *a priori* the exact effect any particular modification, e.g., substitution, deletion, insertion, etc., will have on the biological activity of TANK2. However, one skilled in the art will appreciate that the effect will be evaluated by routine screening assays. For example, a derivative typically is made by linker scanning site-directed mutagenesis of the DNA encoding the native TANK2 molecule. The derivative is then expressed in a recombinant host, and, optionally, purified from the cell culture, for example, by immunoaffinity chromatography. The activity of the cell lysate or the purified derivative is then screened in a suitable screening assay for the desired characteristic. For example, a change in the immunological character of the functional derivative, such as affinity for a given antibody, is measured by a competitive type immunoassay. Changes in other parameters of the expressed product may be measured by the appropriate assay.

Antibodies

The present invention provides antibodies that bind with specificity to a TANK2 polypeptide. An "antibody" as used herein is defined broadly as a protein that characteristically immunoreacts with an epitope (antigenic determinant) that is characteristic of the TANK2 polypeptide. As used herein, an antibody is said to "immunoreact" with an antigen such as a polypeptide if the antibody specifically recognizes and binds an epitope that is characteristic of the antigen by way of one or more variable regions or one or more of the complementarity determining regions (CDRs) of the antibody.

An antibody that is immunoreactive with a given polypeptide may exhibit cross-reactivity to another polypeptide if the two polypeptides each comprise a common structural feature that defines the same characteristic epitope. In the case of related polypeptides, cross-reactivity can correlate to common structural features such as sequence identity, homology, or similarity found among the related polypeptides. Accordingly, families of polypeptides can often be identified by a cross-reactive antibody, i.e., an antibody that immunoreacts with some or all of the members of the polypeptide family sharing the common epitope. Thus, the invention encompasses antibodies that immunoreact with a particular member of the TANK2 family of

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polypeptides, e.g., a polypeptide comprising the amino acid sequence defined by SEQ ID NO:133 or SEQ ID NO:135. The invention further encompasses antibodies that immunoreact with some or all members of the TANK2 family of polypeptides.

Screening assays to determine the binding specificity of an antibody are well known

5 and routinely practiced in the art [see, e.g., Harlow et al. (Eds.), *Antibodies: A Laboratory Manual*, Ch. 6, Cold Spring Harbor Laboratory, Cold Spring Harbor NY (1988)]. The immunoreactive specificity with which an antibody binds to a given polypeptide antigen is to be distinguished from interactions with other proteins, e.g., *Staphylococcus aureus* protein A or other antibodies in ELISA techniques, that are
10 mediated through parts of the antibody other than the variable regions, in particular the constant regions of the antibody.

Antibodies include, for example, monoclonal antibodies, polyclonal antibodies, single chain antibodies (scFv antibodies), chimeric antibodies, multifunctional/multispecific (e.g., bifunctional or bispecific) antibodies, humanized
15 antibodies, human antibodies, and CDR-grafted antibodies (including moieties that include CDR sequences that specifically immunoreact with a polypeptide of the invention). Antibodies according to the invention also include antibody fragments, so long as they exhibit the desired biological activity. "Antibody fragments" comprise a portion of a full-length antibody, generally the antigen binding or variable region
20 thereof. Examples of antibody fragments include Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Antibodies of the invention can be produced by any method known in the art. For example, polyclonal antibodies are isolated from mammals that have been
25 immunized against the protein or a functional analog in accordance with methods known in the art. Briefly, polyclonal antibodies may be produced by injecting an immunogenic TANK2 polypeptide (immunogen) into a host mammal (e.g., rabbit, mouse, rat, or goat). Adjuvants may be employed to increase the immune response. Sera from the host mammal are extracted and screened to obtain polyclonal antibodies
30 that are specific for (immunoreact with) the TANK2 polypeptide.

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Monoclonal antibodies (also referred to herein as “mAbs”) are preferred. As used herein “monoclonal antibody” refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific (“monospecific”), being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations, which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen.

The modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. Monoclonal antibodies may be prepared using any suitable technique capable of yielding a continuous cell line producing a homogeneous antibody. Such methods include the immunological method [Köhler and Milstein, *Nature* 256:495-7 (1975); Campbell, “Monoclonal antibody technology, the production and characterization of rodent and human hybridomas” in Burdon et al. (Eds.), *Laboratory Techniques in Biochemistry and Molecular Biology*, Vol. 13, Elsevier Science Publishers, Amsterdam (1985)] or any similar method. Monoclonal antibodies may also be isolated from phage antibody libraries [Clackson et al., *Nature* 352:624-8 (1991); Marks et al., *J Mol Biol* 222:581-97 (1991)].

To illustrate, to produce monoclonal antibodies a host mammal is immunized by injection of an immunogenic TANK2 polypeptide, and then boosted. Spleens are collected from immunized mammals a few days after the final boost. Cell suspensions from the spleens are fused with a tumor cell line to create immortalized hybrid cell lines or “hybridomas.” Individual clones can be isolated by limiting dilution and then tested for the specificity of the antibodies they produce. Selected cells can then be grown, e.g., by the ascites method, to provide a continuous source of the desired homogeneous antibody.

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Antibodies can be engineered using genetic techniques to produce chimeric antibodies including protein components from two or more species. For use in *in vivo* applications with a human subject, the antibody can be "humanized," i.e., modified to contain an antigen binding region from one species, e.g., a rodent, with the bulk of the antibody replaced with sequences derived from human immunoglobulin. In one method, the non-human CDRs of one species e.g., a mouse or rabbit, are inserted into a framework sequence of another species, e.g., a human, or into a consensus framework sequence. Further changes can then be introduced into the antibody framework to modulate affinity or immunogenicity of the engineered antibody. Methods are also known for inducing expression of engineered antibodies in various cell types, such as mammalian and microbial cell types. Numerous techniques for preparing engineered antibodies are described in the art [e.g., Owens and Young, *J Immunol Meth* 168:149-65 (1994)].

Antibodies further include recombinant polyclonal or monoclonal Fab fragments [e.g., Huse et al., *Science* 246:1275-81 (1989)]. Alternatively, techniques described for the production of single chain antibodies [e.g., US Patent No. 4,946,778] can be adapted to produce TANK2-specific single chain antibodies (e.g., single chain Fv fragments; abbreviated "scFv"). Rapid, large-scale recombinant methods for generating antibodies may be employed, such as phage display or ribosome display methods, optionally followed by affinity maturation [see, e.g., Ouwehand et al., *Vox Sang* 74(Suppl 2):223-32 (1998); Rader et al., *Proc Natl Acad Sci USA* 95:8910-5 (1998); Dall'Acqua et al., *Curr Opin Struct Biol* 8:443-50 (1998)].

Fully human antibodies are especially preferred for therapeutic use in humans, but they are typically difficult to produce. For example, when the immunogen is a human self-antigen, a human will typically not produce any immune response to the antigen. Methods for making fully human antibodies have been developed and are known in the art. Accordingly, fully human antibodies can be produced by using an immunogenic TANK2 polypeptide to immunize an animal (e.g., mouse) that has been transgenically modified to express at least a significant fraction of the human repertoire of immunoglobulin genes [see, e.g., Bruggemann et al., *Immunol Today* 17:391-7 (1996)].

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As noted herein, host cells of the invention are a valuable source of immunogen for development of antibodies specifically immunoreactive with TANK2. To be useful as an immunogen for the preparation of polyclonal or monoclonal antibodies, a TANK2 peptide fragment must contain sufficient amino acid residues to define an immunogenic epitope. If the fragment is too short to be immunogenic *per se*, it may be conjugated to a carrier molecule. Suitable carrier molecules include, for example, keyhole limpet hemocyanin (KLH) and bovine serum albumin (BSA). Conjugation may be carried out by methods known in the art. One such method is to combine a cysteine residue of the fragment with a cysteine residue on the carrier molecule.

Antibodies of the invention are useful for therapeutic methods (by modulating activity of TANK2), diagnostic methods (by detecting TANK2 in a sample), as well as purification of TANK2. The antibodies are particularly useful for detecting and/or quantitating TANK2 expression in cells, tissues, organs, and lysates and extracts thereof, as well as in fluids such as serum, plasma, cerebrospinal fluid, urine, sputum, peritoneal fluid, pleural fluid, or bronchoalveolar lavage fluid. Kits comprising an antibody of the invention for any of the purposes described herein are also contemplated. In general, a kit of the invention also includes a control antigen with which the antibody immunoreacts, and may further include other reagents, containers, and package inserts.

Further, the invention includes neutralizing antibodies, i.e., antibodies that significantly inhibit or impair a biological activity of the proteins or functional analogs of the invention. In particular, neutralizing antibodies inhibit or impair the poly(ADP-ribose) polymerase activity of TANK2. Neutralizing antibodies may be especially desirable for therapeutic and diagnostic applications.

Functional equivalents further include fragments of antibodies that have the same binding characteristics as, or that have binding characteristics comparable to, those of the whole antibody. Such fragments may contain one or both Fab fragments or the F(ab')₂ fragment. Preferably, the antibody fragments contain all six complement determining regions ("CDRs") of the whole antibody, although fragments containing fewer than all of such regions, such as three, four, or five CDRs,

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may also be functional. Fragments may be prepared by methods described in the art [e.g., Lamoyi et al., *J Immunol Meth* 56:235-43 (1983); Parham, *J Immunol* 131:2895-902 (1983)].

Moreover, specific binding proteins can be developed using isolated or recombinant TANK2 products, TANK2 variants, or cells expressing such products. Binding proteins are useful for purifying TANK2 products and detection or quantification of TANK2 products in fluid and tissue samples using known immunological procedures. Binding proteins are also manifestly useful in modulating (i.e., blocking, inhibiting, or stimulating) biological activities of TANK2 polypeptides, especially those activities involved in signal transduction. Thus, neutralizing antibodies that inhibit the activity of TANK2 polypeptides are provided. Anti-idiotypic antibodies specific for anti-TANK2 antibodies are also contemplated.

Detectable Polynucleotide and Polypeptide Probes

The present invention further provides a method of detecting the presence of a TANK2-encoding polynucleotide or a TANK2 polypeptide in a sample. The method involves use of a labeled probe that recognizes the presence of a defined target in the sample. The probe may be an antibody that recognizes a TANK2 polypeptide, or an oligonucleotide that recognizes a polynucleotide encoding TANK2 polypeptide.

The probes of the invention can be detectably labeled in accordance with methods known in the art. In general, the probe can be modified by attachment of a detectable label (reporter) moiety to the probe, or a detectable probe can be manufactured with a detectable label moiety incorporated therein. The detectable label moiety can be any detectable moiety, many of which are known in the art, including radioactive atoms, electron dense atoms, enzymes, chromogens and colored compounds, fluorogens and fluorescent compounds, members of specific binding pairs, and the like.

Methods for labeling oligonucleotide probes have been described in the art [see, e.g., Leary et al., *Proc Natl Acad Sci USA* 80:4045-49 (1983); Renz and Kurz, *Nucleic Acids Res* 12:3435-44 (1984); Richardson and Gumpert, *Nucleic Acids Res* 11:6167-84 (1983); Smith et al., *Nucleic Acids Res* 13:2399-412 (1985); Meinkoth

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and Wahl, *Anal Biochem* 138:267-84 (1984); and US Patent Nos. 4,711,955; 4,687,732; 5,241,060; 5,244,787; 5,328,824; 5,580,990; and 5,714,327].

Methods for labeling antibodies have been also been described [see, e.g., Hunter et al., *Nature* 144:495-6 (1962); David et al., *Biochemistry* 13:1014-21 (1974);
5 and US Patent Nos. 3,940,475 and 3,645,090].

The label moiety may be radioactive. Some examples of useful radioactive labels include ^{32}P , ^{125}I , ^{131}I , and ^3H . Use of radioactive labels has been described [e.g., UK patent document 2,034,323 and US Patent Nos. 4,358,535 and 4,302,204].

Some examples of non-radioactive labels include enzymes, chromogens,
10 atoms and molecules detectable by electron microscopy, and metal ions detectable by their magnetic properties.

Some useful enzymatic labels include enzymes that cause a detectable change in a substrate. Some useful enzymes (and their substrates) include, for example, horseradish peroxidase (pyrogallol and o-phenylenediamine), beta-galactosidase
15 (fluorescein beta-D-galactopyranoside), and alkaline phosphatase (5-bromo-4-chloro-3-indolyl phosphate/nitro blue tetrazolium). The use of enzymatic labels has been described in the art [see, e.g., UK patent document 2,019,404, European patent document EP 63,879, and Rotman, *Proc Natl Acad Sci USA* 47:1981-91 (1961)].

Useful reporter moieties include, for example, fluorescent, phosphorescent, chemiluminescent, and bioluminescent molecules, as well as dyes. Some specific colored or fluorescent compounds useful in the present invention include, for example, fluoresceins, coumarins, rhodamines, Texas red, phycoerythrins, umbelliferones, Luminol®, and the like. Chromogens or fluorogens, i.e., molecules
25 that can be modified (e.g., oxidized) to become colored or fluorescent or to change their color or emission spectra, are also capable of being incorporated into probes to act as reporter moieties under particular conditions.

The label moieties may be conjugated to the probe by methods that are well known in the art. The label moieties may be directly attached through a functional
30 group on the probe. The probe either contains or can be caused to contain such a

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functional group. Some examples of suitable functional groups include, for example, amino, carboxyl, sulfhydryl, maleimide, isocyanate, isothiocyanate.

Alternatively, label moieties such as enzymes and chromogens may be conjugated to antibodies or nucleotides by means of coupling agents, such as dialdehydes, carbodiimides, dimaleimides, and the like.

The label moiety may also be conjugated to the probe by means of a ligand attached to the probe by a method described above and a receptor for that ligand attached to the label moiety. Any of the known ligand-receptor binding pair combinations is suitable. Some suitable ligand-receptor pairs include, for example, biotin-avidin or -streptavidin, and antibody-antigen. The biotin-streptavidin combination may be preferred.

Methods of Using Tankyrase2 Polynucleotides and Polypeptides

The scientific value of the information contributed through the disclosures of DNA and amino acid sequences of the present invention is manifest. As one series of examples, knowledge of the sequence of a cDNA for tank2 makes possible through use of Southern hybridization or polymerase chain reaction (PCR) the identification of genomic DNA sequences encoding TANK2 and TANK2 expression control regulatory sequences. DNA/DNA hybridization procedures carried out with DNA sequences of the invention under moderately to highly stringent conditions are also expected to allow the isolation of DNAs encoding allelic variants of TANK2.

Similarly, non-human species genes encoding proteins homologous to TANK2 can also be identified by Southern and/or PCR analysis. As an alternative, complementation studies can be useful for identifying other human TANK2 products as well as non-human proteins, and DNAs encoding the proteins, sharing one or more biological properties of TANK2. Oligonucleotides of the invention are also useful in hybridization assays to detect the capacity of cells to express TANK2.

Polynucleotides of the invention may also be the basis for diagnostic methods useful for identifying a genetic alteration in the tank2 locus that underlies a disease state.

For example, the differential expression or activity of TANK2-LONG and TANK2-SHORT may be capable of correlation with particular disease state(s), rendering one

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or both forms of TANK2 suitable as diagnostic markers or as therapeutic targets as described herein. Therefore, selective reagents, e.g., oligonucleotides that selectively hybridize to one form of tank2 or antibodies that selectively immunoreact with one form of TANK2, may be especially useful.

5 Oligonucleotides of the invention, as described herein, may be used in methods to amplify DNA for various purposes. "Amplification" according to the method of the invention refers to any molecular biology technique for detection of trace levels of a specific nucleic acid sequence by exponentially amplifying a template nucleic acid sequence. In particular, suitable amplification techniques include such
10 techniques as the polymerase chain reaction (PCR), the ligase chain reaction (LCR) and variants thereof. PCR is known to be a highly sensitive technique, and is in wide use [see, e.g., Innis et al., *PCR Protocols: A Guide to Methods and Applications*, Academic Press, Inc., San Diego (1990); Dieffenbach and Dveksler, *PCR Primer: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Plainview NY (1995); and
15 US Patents Nos. 4,683,195; 4,800,195; and 4,965,188]. The more recently developed LCR technique is known to be highly specific, and is capable of detecting point mutations [see, e.g., Landegren et al., *Science* 241:1077-80 (1988) and Barany et al., *PCR Methods and Applications* 1:5-16 (1991)]. An LCR kit is available from Stratagene. In certain circumstances, it is desirable to couple the PCR and LCR
20 techniques to improve precision of detection. Other amplification techniques may be employed in accordance to the invention.

 Oligonucleotide amplification primers are often provided as matched pairs of single-stranded oligonucleotides; one with sense orientation (5' → 3') and one with antisense (3' ← 5') orientation. Such specific primer pairs can be employed under
25 optimized conditions for identification of a specific gene or condition. Alternatively, the same primer pair, nested sets of oligomers, or even a degenerate pool of oligomers, may be employed under less stringent conditions for detection and/or quantitation of closely related DNA or RNA sequences.

 Such oligonucleotides can be used in various methods known in the art to
30 extend the specified nucleotide sequences. These methods permit use of a known

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sequence to determine unknown adjacent sequence, thereby enabling detection and determination of upstream sequences such as promoters and regulatory elements.

For example, restriction-site polymerase chain reaction is a direct method that uses universal primers to retrieve unknown sequence adjacent to a known locus [see, 5 e.g., Gobinda et al., *PCR Methods Applic* 2:318-22 (1993)]. In this method, genomic DNA is first amplified in the presence of primer to a linker sequence and a primer specific to the known region. The amplified sequences are subjected to a second round of PCR with the same linker primer and another specific primer internal to the first one. Products of each round of PCR are transcribed with an appropriate RNA 10 polymerase and sequenced using reverse transcriptase.

Inverse PCR can be used to amplify or extend sequences using divergent primers based on a known region [Triglia et al., *Nucleic Acids Res* 16:8186 (1988)]. The primers may be designed using Oligo 4.0 (National Biosciences, Inc., Plymouth, MN), or another appropriate program, to be 22-30 nucleotides in length, to have a GC 15 content of 50% or more, and to anneal to the target sequence at temperatures about 68°-72°C. This method uses several restriction enzymes to generate a suitable fragment in the known region of a gene. The fragment is then circularized by intermolecular ligation and used as a PCR template.

Capture PCR is a method for PCR amplification of DNA fragments adjacent 20 to a known sequence in human and yeast artificial chromosome (YAC) DNA [Lagerstrom et al., *PCR Methods Applic* 1:111-9 (1991)]. Capture PCR also requires multiple restriction enzyme digestions and ligations to place an engineered double-stranded sequence into an unknown portion of the DNA molecule before PCR. Walking PCR is a method for targeted gene walking that permits retrieval of unknown 25 sequence [Parker et al., *Nucleic Acids Res* 19:3055-60 (1991)]. The PromoterFinder™ kit (Clontech, Palo Alto, CA) uses PCR, nested primers, and special libraries to "walk in" genomic DNA. This process avoids the need to screen libraries and is useful in finding intron/exon junctions.

Such methods can be used to explore genomic libraries to extend 5' sequence 30 and to obtain endogenous tank2 genomic sequence, including elements such as promoters, introns, operators, enhancers, repressors, and the like. Preferred libraries

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for screening for full-length cDNAs are ones that have been size-selected to include larger cDNAs. In addition, randomly primed libraries are preferred in that they will contain more sequences that contain the 5' and upstream regions of genes.

The oligonucleotide probes may also be used for mapping the endogenous
5 genomic sequence. The sequence may be mapped to a particular chromosome or to a specific region of the chromosome using well known techniques. These include *in situ* hybridization to chromosomal spreads [Venna et al., *Human Chromosomes: A Manual of Basic Technique*, Pergamon Press, New York NY (1988)], flow-sorted chromosomal preparations, or artificial chromosome constructions such as YACs,
10 bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries.

Hybridization of chromosomal preparations and physical mapping techniques such as linkage analysis using established chromosomal markers are invaluable in extending genetic maps. Examples of genetic maps can be found in the art [e.g.,
15 Hodgkin et al., *Science* 270:410-4 (1995) and Murray et al., *Science* 265:2049-54 (1994)]. Often the placement of a gene on the chromosome of another mammalian species may reveal associated markers even if the number or arm of a particular human chromosome is not known. Such sequences can be assigned to particular structural features of chromosomes by physical mapping. This provides valuable
20 information to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once a disease or syndrome has been crudely localized by genetic linkage to a particular genomic region, any sequences mapping to that area may represent associated or regulatory genes for further investigation. See, e.g., Gatti et al., *Nature* 336:577-80 (1988). The polynucleotides of the invention may
25 also be used to detect differences in the chromosomal location due to translocation, inversion, etc., between normal, carrier, or affected individuals. Other types of genetic maps can also be developed, e.g., physical maps of the genome based on sequence-tagged sites (STS) [see, e.g., Hudson et al., *Science* 270:1945-54 (1995)].

The DNA sequence information provided by the present invention also makes
30 possible the development, e.g., through homologous recombination or "knock-out" strategies [Capecchi, *Science* 244:1288-92 (1989)], of animals that fail to express

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functional TANK2 or that express a variant of TANK2. Such animals are useful as models for studying the *in vivo* activities of TANK2 and modulators thereof.

As described herein, the invention provides antisense nucleic acid sequences that recognize and hybridize to polynucleotides encoding TANK2. Modifications of gene expression can be obtained by designing antisense sequences to the control regions of the tank2 gene, such as the promoters, enhancers, and introns. Oligonucleotides derived from the transcription initiation site, e.g., between -10 and +10 regions of the leader sequence, are preferred. Antisense RNA and DNA molecules may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes. The worker of ordinary skill will appreciate that antisense molecules of the invention include those that specifically recognize and hybridize to tank2 DNA (as determined by sequence comparison of tank2 DNA to DNA encoding other known molecules). The antisense molecules of the invention also include those that recognize and hybridize to DNA encoding other members of the TANK2 family of proteins. Antisense polynucleotides that hybridize to multiple DNAs encoding other members of the TANK2 family of proteins are also identifiable through sequence comparison to identify characteristic or signature sequences for the family of TANK2 proteins. Accordingly, such antisense molecules preferably have at least 95%, more preferably at least 98%, and still more preferably at least 99% identity to the target tank2 sequence.

Antisense polynucleotides are particularly relevant to regulating expression of TANK2 by those cells expressing tank2 mRNA. Antisense polynucleotides (preferably 10 to 20 bp oligonucleotides) capable of specifically binding to tank2 expression control sequences or tank2 RNA are introduced into cells, e.g., by a viral vector or a colloidal dispersion system such as a liposome. The antisense oligonucleotide binds to the tank2 target nucleotide sequence in the cell and prevents transcription or translation of the target sequence. Phosphorothioate and methylphosphonate antisense oligonucleotides are specifically contemplated for therapeutic use under the invention. The antisense oligonucleotides may be further

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modified by poly-L-lysine, transferrin polylysine, or cholesterol moieties at their 5' ends [for a recent review of antisense technology, see Delihias et al., *Nat Biotechnol* 15:751-3 (1997)].

5 The invention further comprises methods to modulate TANK2 expression by means of ribozyme technology [for a review, see Gibson and Shillito, *Mol Biotechnol* 7:125-37 (1997)]. Ribozyme technology can be used to inhibit translation of tank2 mRNA in a sequence specific manner through (i) the hybridization of a complementary RNA to a target mRNA and (ii) cleavage of the hybridized mRNA through endonuclease activity inherent to the complementary RNA. Ribozymes can be identified by empirical methods such as using complementary oligonucleotides in
10 ribonuclease protection assays, but more preferably are specifically designed based on scanning the target molecule for accessible ribozyme cleavage sites [Bramlage et al., *Trends Biotechnol* 16:434-8 (1998)]. Delivery of ribozymes to target cells can be accomplished using either exogenous or endogenous delivery techniques well known and practiced in the art. Exogenous can include use of targeting liposomes or direct
15 local injection. Endogenous methods include use of viral vectors and non-viral plasmids.

Ribozymes can specifically modulate expression of TANK2 when designed to be complementary to regions unique to a polynucleotide encoding TANK2.
20 "Specifically modulate," therefore is intended to mean that ribozymes of the invention recognize only a polynucleotide encoding TANK2. Similarly, ribozymes can be designed to modulate expression of all or some of the TANK2 family of proteins. Ribozymes of this type are designed to recognize nucleotide sequences conserved all or some of the polynucleotides encoding the TANK2 family members.

25 The invention further embraces methods to modulate transcription of tank2 through use of oligonucleotide-directed triple helix formation (also known as Hogeboom base-pairing methodology) [for a review, see Lavrovsky et al., *Biochem Mol Med* 62:11-22 (1997)]. Triple helix formation is accomplished using sequence-specific oligonucleotides that hybridize to double stranded DNA in the major groove
30 as defined in the Watson-Crick model. This triple helix hybridization compromises the ability of the original double helix to open sufficiently for the binding of

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polymerases, transcription factors, or regulatory molecules. Preferred target sequences for hybridization include promoter and enhancer regions to permit transcriptional regulation of TANK2 expression. Oligonucleotides that are capable of triple helix formation can alternatively be coupled to DNA damaging agents, which
5 can then be used for site-specific covalent modification of target DNA sequences [see Lavrovsky et al., *supra*].

Both antisense RNA and DNA molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of RNA molecules. These include techniques for chemically synthesizing oligonucleotides such as solid-
10 phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by *in vitro* or *in vivo* transcription of DNA sequences encoding the antisense RNA molecule. Such DNA sequences may be incorporated into a variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, antisense cDNA constructs that synthesize antisense RNA constitutively or inducibly
15 can be introduced into cell lines, cells, or tissues.

Mutations in a gene that result in loss of normal function of the gene product may underlie TANK2-related disease states. The invention comprehends gene therapy to restore TANK2 activity as indicated in treating those disease states characterized by a deficiency or absence of poly(ADP-ribose) polymerase activity
20 associated with the TANK2 enzyme. Delivery of functional tank2 gene to appropriate cells is effected *ex vivo*, *in situ*, or *in vivo* by use of vectors, and more particularly viral vectors (e.g., adenovirus, adeno-associated virus, or retrovirus), or *ex vivo* by use of physical DNA transfer methods (e.g., liposomes or chemical treatments) [see, e.g., Anderson, *Nature* 392(6679 Suppl):25-30 (1998)]. Alternatively, it is contemplated
25 that in other disease states, preventing the expression or inhibiting the activity of TANK2 will be useful in treating those disease states. Antisense therapy or gene therapy can be applied to negatively regulate the expression of TANK2.

The DNA and amino acid sequence information provided by the present invention also makes possible the systematic analysis of the structure and function of
30 TANK2 proteins. DNA and amino acid sequence information for TANK2 also permits identification of molecules with which a TANK2 polypeptide will interact.

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Agents that modulate (i.e., increase, decrease, or block) TANK2 activity may be identified by incubating a putative modulator with TANK2 and determining the effect of the putative modulator on TANK2 activity. The selectivity of a compound that modulates the activity of the TANK2 polypeptide can be evaluated by comparing its activity on the TANK2 to its activity on other proteins.

Numerous methods are amenable to modification by including TANK2 polypeptides or tank2 polynucleotides of the invention, including cell based methods such as dihybrid and trihybrid screens to detect binding partners and split hybrid screens to detect compounds that disrupt complexing of binding partners. Other methods include *in vitro* methods, such as assays in which a TANK2 polypeptide, tank2 polynucleotide, or a binding partner thereof is immobilized, as well as solution assays, are contemplated under the invention. These methods are exemplified by a general approach that includes the steps of contacting a TANK2 polypeptide with a putative binding partner compound, detecting or measuring binding of the TANK2 polypeptide with the compound, and optionally isolating and/or identifying the binding partner compound.

Cell-based assays include methods of screening genomic DNA or cDNA libraries to identify binding partners of TANK2 polypeptides. Exemplary methods include the dihybrid or two-hybrid screen [Fields and Song, *Nature* 340:245-6 (1989); Fields, *Methods: A Companion to Methods in Enzymology* 5:116-24 (1993)] which can be used identify DNAs encoding binding partners. Modifications and variations of the dihybrid assay are described [Colas and Brent, *Trends Biotechnol* 16:355-63 (1998)]. Trihybrid screens can also be employed [Fuller et al., *Biotechniques* 25:85-8, 90-2 (1998)].

Cell-based methods of the invention may be used to identify components in biological pathways that are mediated by TANK2 biological activity. In one aspect, the method is carried out in a host cell containing a soluble TANK2 polypeptide and a soluble form of its binding partner and wherein decreased or increased binding is quantitated through measurement of a binding-dependent phenotypic change in the host cell that is associated with a change in expression of a reporter gene product.

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Alternatively, cell-based assays to identify inhibitors of TANK2 polypeptide interaction with a known binding partner may be based on methods such as the split hybrid assay [PCT patent publication WO 98/13502] and variations thereof [PCT patent publication WO 95/20652].

5 *In vitro* methods can comprise the steps of (a) contacting an immobilized TANK2 polypeptide with a candidate binding partner compound, and (b) detecting binding of the candidate compound to the TANK2 polypeptide. In an alternative embodiment, the candidate binding partner compound is immobilized and binding of the TANK2 polypeptide is detected. Immobilization may be accomplished using any
10 of the methods well known in the art, including bonding to a support, beads, or a chromatographic resin, as well as high affinity interactions such as antibody binding or use of an avidin:biotin type system. Detection of binding of the ligands can be accomplished, for example, by (i) using a detectable (e.g., radioactive or fluorescent) label on the ligand that is not immobilized, (ii) using an antibody immunospecific for
15 the non-immobilized ligand, (iii) using a label on the non-immobilized ligand that promotes excitation of a fluorescent support to which the immobilized ligand is bound, as well as other techniques routinely practiced in the art.

In solution assays, methods of the invention comprise the steps of (a) contacting a TANK2 polypeptide with one or more candidate binding partner
20 compounds, and (b) identifying the compounds that bind to the TANK2 polypeptide. Identification of the compounds that bind TANK2 can be achieved by isolating the TANK2:binding partner complex, and separating the TANK2 polypeptide from the binding partner compound. An additional step of characterizing the physical, biological, or biochemical properties of the binding partner compound is also
25 comprehended under the invention. In one approach the TANK2:binding partner complex is isolated using a second binding partner compound (e.g., an antibody or other protein) that interacts with either of the principal ligands in the complex.

Selective modulators may include, for example, antibodies and other proteins or peptides that selectively or specifically bind to a TANK2 polypeptide or a TANK2-
30 encoding polynucleotide, oligonucleotides that selectively or specifically bind to TANK2 polypeptides or TANK2-encoding polynucleotides, and other non-peptide

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compounds (e.g., isolated or synthetic organic molecules) that selectively or specifically react with TANK2 polypeptides or TANK2-encoding polynucleotides. Modulators also include compounds as described above but which interact with a specific binding partner of TANK2 polypeptides. Mutant forms of TANK2, such as those that affect the biological activity or cellular location of the wild-type TANK2, are also contemplated under the invention. Presently preferred targets for the development of selective modulators include, for example:

- (1) cytoplasmic or transmembrane regions of TANK2 polypeptides that contact other proteins and/or localize TANK2 within a cell, e.g., to telomeres;
- (2) extracellular regions of TANK2 polypeptides that bind specific binding partners;
- (3) regions of the TANK2 polypeptides that bind substrate, i.e., ADP-ribose;
- (4) allosteric regulatory sites of the TANK2 polypeptides;
- (5) regions of the TANK2 polypeptides that mediate multimerization;
- (6) regions of TANK2 or other proteins (e.g., TRF1 or TRF2) that act as acceptors ADP-ribosylation.

Still other selective modulators include those that recognize particular regulatory or TANK2-encoding nucleotide sequences. Selective and specific modulators of TANK2 activity may be therapeutically useful in treatment of a wide range of diseases and physiological conditions in which aberrant TANK2 activity is involved.

A TANK2-encoding polynucleotide sequence may be used for the diagnosis of diseases resulting from or associated with TANK2 expression or activity. For example, polynucleotide sequences encoding a TANK2 polypeptide (e.g., TANK2-LONG or TANK2-SHORT) may be used in hybridization or PCR assays of biological samples, e.g., samples or extracts of fluids or tissues from biopsies or autopsies, to detect abnormalities in TANK2 expression. Such qualitative or quantitative methods may include Southern or northern analysis, dot blot, or other membrane-based technologies; PCR technologies; dipstick, pin or chip technologies; and ELISA or other multiple-sample format technologies. These types of techniques are well known in the art and have been employed in commercially available diagnostic kits.

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Such assays may be tailored to evaluate the efficacy of a particular therapeutic treatment regimen and may be used in animal studies, in clinical trials, or in monitoring the treatment of an individual patient. To provide a basis for the diagnosis of disease, a normal or standard profile for TANK2 expression must be established.

- 5 This is accomplished by combining a biological sample taken from a normal subject with a tank2 polynucleotide, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained for normal subjects with a dilution series of positive controls run in the same experiment where a known amount of a purified tank2 polynucleotide is used.
- 10 Standard values obtained from normal samples may be compared with values obtained from samples from subjects potentially affected by a disorder or disease related to TANK2 expression. Deviation between standard and subject values establishes the presence of the disease state. If disease is established, an existing therapeutic agent is administered, and treatment profile or values may be generated.
- 15 The assay may be repeated on a regular basis to evaluate whether the values progress toward or return to the normal or standard pattern. Successive treatment profiles may be used to show the efficacy of treatment over a period of several days or several months.

- Anti-TANK2 antibodies are useful for the diagnosis of conditions, disorders,
- 20 or diseases characterized by or associated with abnormal expression of a TANK2 polypeptide. Diagnostic assays for TANK2 polypeptides include methods that employ a labeled antibody to detect a TANK2 polypeptide in a biological sample such as a body fluid, cells, tissues, sections, or extracts of such materials. The polypeptides and antibodies of the present invention may be used with or without modification.
- 25 Preferably, the polypeptide or the antibody will be labeled by linking them, either covalently or non-covalently, with a detectable label moiety as described herein.

- Antibody-based methods for detecting the presence of TANK2 polypeptides in biological samples are enabled by virtue of the present invention, including assays for differential detection of TANK2-LONG versus TANK2-SHORT. Assays for
- 30 detecting the presence of proteins with antibodies have been previously described, and follow known formats, such as enzyme-linked immunosorbent assay (ELISA),

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radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS) and flow cytometry, western blots, sandwich assays, and the like. These formats are normally based on incubating an antibody with a sample suspected of containing the TANK2 protein and detecting the presence of a complex between the antibody and the protein.

5 The antibody is labeled either before, during, or after the incubation step. The specific concentrations of antibodies, the temperature and time of incubation, as well as other such assay conditions, can be varied, depending upon various factors including the concentration of antigen in the sample, the nature of the sample, etc. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation [see, e.g., Hampton et al.,
10 *Serological Methods: A Laboratory Manual*, APS Press, St Paul, MN (1990)].

To provide a basis for the quantitation of TANK2 protein in a sample or for the diagnosis of disease, normal or standard values of TANK2 polypeptide expression must be established. This is accomplished by combining body fluids or cell extracts
15 taken from a normal sample or from normal subjects, either animal or human, with antibody to a TANK2 polypeptide. The amount of standard complex formation may be quantified by comparing it with a dilution series of positive controls where a known amount of antibody is combined with known concentrations of a purified TANK2 polypeptide. Then, standard values obtained from normal samples may be
20 compared with values obtained from samples from test sample, e.g., subjects potentially affected by a disorder or disease related to a TANK2 expression. Deviation between standard and test values establishes the presence of the disease state.

25 Methods for Identifying Modulators of Tankyrase2 Activity

The TANK2 protein, as well as fragments thereof possessing biological activity can be used for screening putative modulator compounds in any of a variety of drug screening techniques. The term "modulator" as used herein refers to a compound that acts as an agonist or as an antagonist of TANK2 activity. Modulators
30 according to the invention include allosteric modulators of activity as well as inhibitors of activity. An "agonist" of TANK2 is a compound that enhances or

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increases the ability of TANK2 to carry out any of its biological functions. An example of such an agonist is an agent that increases the ability of TANK2 to bind to damaged DNA or to polymerize ADP-ribose. An "antagonist" of TANK2 is a compound that diminishes or abolishes the ability of TANK2 to carry out any of its biological functions. An example of such antagonists is an anti-TANK2 antibody.

Accordingly, the invention provides a method for screening a plurality of test compounds for specific binding affinity with a TANK2 polypeptide, comprising providing a plurality of test compounds; combining a TANK2 polypeptide with each of the plurality of test compounds for a time sufficient to allow binding under suitable conditions; and detecting binding of the TANK2 polypeptide to each of the plurality of test compounds, thereby identifying those test compounds that specifically bind the TANK2 polypeptide.

The present invention also provides a method of identifying a modulator of a biological activity of a TANK2 polypeptide, comprising the steps of a) contacting the compound with a TANK2 polypeptide, b) incubating the mixture of step a) with a substrate under conditions suitable for the biological activity, c) measuring the amount of the biological activity; and d) comparing the amount of biological activity of step c) with the amount of biological activity obtained with the TANK2 polypeptide, incubated without the compound, thereby determining whether the compound stimulates or inhibits the biological activity. In one embodiment of the method, the TANK2 polypeptide is a fragment from the non-catalytic region of the TANK2 and provides a method to identify allosteric modulators of TANK2. In another embodiment, the TANK2 polypeptide is a fragment from the catalytic region of TANK2 and provides a method to identify inhibitors of the biological activity. TANK2-LONG and TANK2-SHORT polypeptides or specific fragments thereof may be employed.

Accordingly, the polypeptide employed in such methods may be free in solution, affixed to a solid support, displayed on a cell surface, or located intracellularly. The modulation of activity or the formation of binding complexes between the TANK2 polypeptide and the agent being tested may be measured. TANK2 polypeptides are amenable to biochemical or cell-based high throughput

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screening (HTS) assays according to methods known and practiced in the art, including melanophore assay systems to investigate receptor-ligand interactions, yeast-based assay systems, and mammalian cell expression systems [for a review, see Jayawickreme and Kost, *Curr Opin Biotechnol* 8:629-34 (1997)]. Automated and
5 miniaturized HTS assays are also comprehended [e.g., Houston and Banks, *Curr Opin Biotechnol* 8:734-40 (1997)].

Such HTS assays are used to screen libraries of compounds to identify particular compounds that exhibit a desired property. Any library of compounds may be used, including chemical libraries, natural product libraries, combinatorial libraries
10 comprising random or designed oligopeptides, oligonucleotides, or other organic compounds.

Chemical libraries may contain known compounds, proprietary structural analogs of known compounds, or compounds that are identified from natural product screening.

15 Natural product libraries are collections of materials isolated from natural sources, typically, microorganisms, animals, plants, or marine organisms. Natural products are isolated from their sources by fermentation of microorganisms followed by isolation and extraction of the fermentation broths or by direct extraction from the microorganisms or tissues (plants or animal) themselves. Natural product libraries
20 include polyketides, non-ribosomal peptides, and variants (including non-naturally occurring variants) thereof [for a review, see Cane et al., *Science* 282:63-8 (1998)].

Combinatorial libraries are composed of large numbers of related compounds, such as peptides, oligonucleotides, or other organic compounds as a mixture. Such compounds are relatively straightforward to design and prepare by traditional
25 automated synthesis protocols, PCR, cloning or proprietary synthetic methods. Of particular interest are peptide and oligonucleotide combinatorial libraries.

Still other libraries of interest include peptide, protein, peptidomimetic, multiparallel synthetic collection, recombinatorial, and polypeptide libraries [for a review of combinatorial chemistry and libraries created thereby, see Myers, *Curr Opin*
30 *Biotechnol* 8:701-7 (1997)].

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Once compounds have been identified that show activity as modulators of TANK2 function, a program of optimization can be undertaken in an effort to improve the potency and or selectivity of the activity. This analysis of structure-activity relationships (SAR) typically involves of iterative series of selective
5 modifications of compound structures and their correlation to biochemical or biological activity. Families of related compounds can be designed that all exhibit the desired activity, with certain members of the family potentially qualifying as therapeutic candidates.

The invention also encompasses the use of competitive drug screening assays
10 in which neutralizing antibodies capable of binding a TANK2 polypeptide specifically compete with a test compound for binding to the TANK2 polypeptide. In this manner, the antibodies can be used to detect the presence of any compound, e.g., another peptide that shares one or more antigenic determinants with the TANK2 polypeptide.

15 Therapeutic Uses of TANK2-Encoding Polynucleotides and TANK2 Polypeptides

The invention provides a method for inhibiting the expression or activity of TANK2 therapeutically or prophylactically in a human or other animal. The method comprises administering a TANK2 antagonist in an amount effective for inhibiting
20 TANK2 expression or activity. The invention thus provides a method for treating tissue damage resulting from cell damage or death due to necrosis or apoptosis, comprising administering to the animal an effective amount of a compound that inhibits TANK2 activity. This method may be employed in treating animals that are or may be subject to any disorder whose symptoms or pathology is mediated by
25 TANK2 expression or activity. Antagonists having specificity for TANK2-LONG or TANK2-SHORT may have particular utility in diseases whose pathology or symptoms are mediated by a specific form of TANK2.

The method may further involve administering an antagonist of another poly(ADP-ribose) polymerase activity, such as activity associated with the enzymes
30 PARP, tankyrase 1, and the like. Exemplary PARP antagonists suitable for use in this embodiment include, for example, the compounds described by Banasik et al. [*J Biol*

Chem 267:1569-75 (1992)]. Other exemplary compounds include those described in PCT patent publications WO 99/11623 and WO 99/11649. Alternatively, the TANK2 inhibitory method may entail use of a compound that antagonizes both TANK2 and another enzyme having poly(ADP-ribose) polymerase activity.

5 “Treating” as used herein refers to preventing a disorder from occurring in an animal that may be predisposed to the disorder, but has not yet been diagnosed as having it; inhibiting the disorder, i.e., arresting its development; relieving the disorder, i.e., causing its regression, or ameliorating the disorder, i.e., reducing the severity of symptoms associated with the disorder. “Disorder” is intended to encompass medical
10 disorders, diseases, conditions, syndromes, and the like, without limitation.

 The methods of the invention embrace various modes of treating an animal in which TANK2 is expressed, and in which TANK2-mediated disorders may be treated. Animals treatable according to the invention include mammals (including humans) and non-mammalian animals, e.g., birds, fish, reptiles, and amphibians. Among the
15 non-human mammals that may be treated are companion animals (pets) including dogs and cats; farm animals including cattle, horses, sheep, pigs, and goats; laboratory animals including rats, mice, rabbits, guinea pigs, and primates. The method is most preferably employed in the treatment of TANK2-mediated disorders in humans.

 In particular, the method of the invention may be employed to treat animals
20 therapeutically or prophylactically who are or may be subject to a disorder associated with excessive or undesirable telomerase activity. One aspect of the present invention derives from the ability of TANK2 and its functional derivatives to interact with damaged DNA and to modulate the activity of telomere repeat binding factors (e.g., TRF1 and TRF2).

25 Excessive telomerase activity in cells has been shown to correlate with induction of apparently unlimited capacity of the cells to replicate. In addition, evidence exists that telomerase activity is higher in tumor tissue than most normal tissues suggesting that increased telomerase activity may be essential for tumor growth. Accordingly, the invention also provides to a method of inhibiting oncogenic
30 transformation or inhibiting neoplastic tissue growth, e.g., cancer, in an animal, comprising administering to the animal an effective amount of a compound that

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inhibits TANK2 activity. In this embodiment, the method may further comprise adjuvant administration of a chemotherapeutic or anti-cancer drug and/or radiation therapy.

5 Tumors or neoplasms include new growths of tissue in which the multiplication of cells is uncontrolled and progressive. Some such growths are benign, but others are termed "malignant," leading to death of the organism. Malignant neoplasms or "cancers" are distinguished from benign growths in that, in addition to exhibiting aggressive cellular proliferation, cancers invade surrounding tissues and metastasize. Moreover, malignant neoplasms are characterized in that
10 they show a greater loss of differentiation (greater "dedifferentiation"), and of their organization relative to one another and their surrounding tissues. This property is also called "anaplasia."

Neoplasms treatable by the present invention include solid tumors, i.e., carcinomas and sarcomas. Carcinomas include those malignant neoplasms derived
15 from epithelial cells which tend to infiltrate (invade) the surrounding tissues and give rise to metastases. Adenocarcinomas are carcinomas derived from glandular tissue or in which the tumor cells form recognizable glandular structures. Another broad category of cancers includes sarcomas, which are tumors whose cells are embedded in a fibrillar or homogeneous substance like embryonic connective tissue. The invention
20 also enables treatment of cancers of the myeloid or lymphoid systems, including leukemias, lymphomas and other cancers that typically do not present as a tumor mass, but are distributed in the vascular or lymphoreticular systems.

The type of cancer or tumor cells amenable to treatment according to the invention include, for example, ACTH-producing tumor, acute lymphocytic leukemia,
25 acute nonlymphocytic leukemia, cancer of the adrenal cortex, bladder cancer, brain cancer, breast cancer, cervical cancer, chronic lymphocytic leukemia, chronic myelocytic leukemia, colorectal cancer, cutaneous T-cell lymphoma, endometrial cancer, esophageal cancer, Ewing's sarcoma, gallbladder cancer, hairy cell leukemia, head and neck cancer, Hodgkin's lymphoma, Kaposi's sarcoma, kidney cancer, liver
30 cancer, lung cancer (small and non-small cell), malignant peritoneal effusion, malignant pleural effusion, melanoma, mesothelioma, multiple myeloma,

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neuroblastoma, glioma, non-Hodgkin's lymphoma, osteosarcoma, ovarian cancer, ovarian (germ cell) cancer, pancreatic cancer, penile cancer, prostate cancer, retinoblastoma, skin cancer, soft tissue sarcoma, squamous cell carcinomas, stomach cancer, testicular cancer, thyroid cancer, trophoblastic neoplasms, uterine cancer, vaginal cancer, cancer of the vulva, and Wilm's tumor.

As noted above, regulation of telomere structure appears to be associated with aging. Drugs that modulate the regulation of telomere structure can be expected to have utility in treatment of age-related syndromes or in cases of genetically determined premature aging and premature senility syndromes e.g., progeria (Hutchinson-Gilford progeria syndrome), Werner's syndrome, and other such disorders. Accordingly, the invention provides a method of enhancing the activity of TANK2 in animals suffering from such syndromes. The method may be expected to decrease TRF binding to the telomeres, which in turn promotes increased telomerase activity.

Shortening of telomeres beyond a critical length results in the induction of senescence in many cell types. As telomerase activity is frequently required for maintenance of telomere length, and since TANK2 inhibition may diminish telomerase function, the invention provides for treatment of non-neoplastic proliferative disorders in which TANK2 antagonists may be useful to induce shortened telomeres and cellular senescence. Proliferative disorders include, but are not limited to, andrestenosis, diabetic retinopathy, mesangial proliferative disorder, proliferative glomerulonephritis, polycythemia, myelofibrosis, post-transplantation lymphoproliferative disorder, endometriosis, craniosynostosis, immunoproliferative small intestinal disease, thymic lymphoproliferative disease, myelodysplastic disorders, myeloproliferative disorders, von Willebrand's disease, and proliferative nephritis.

In addition, TANK2 inhibitors may be useful in any inflammatory disorder, including autoimmune disorders, in which proliferation of lymphocytes plays a role. "Inflammatory disorder" as used herein can refer to any disease, disorder, or syndrome in which an excessive or unregulated inflammatory response leads to excessive inflammatory symptoms, host tissue damage, or loss of tissue function.

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"Inflammatory disorders" can also refer to pathological states mediated by influx of leukocytes and or neutrophil chemotaxis.

5 "Inflammation" as used herein refers to a localized, protective response elicited by injury or destruction of tissues, which serves to destroy, dilute or wall off (sequester) both the injurious agent and the injured tissue. Inflammation is notably associated with influx of leukocytes and or neutrophil chemotaxis. Inflammation may result from infection with pathogenic organisms and viruses and from noninfectious means such as trauma or reperfusion following myocardial infarction or stroke, immune response to foreign antigen, and autoimmune responses. Inflammatory
10 disorders amenable to the invention encompass disorders associated with reactions of the specific defense system as well as with reactions of the non-specific defense system.

Accordingly, the present invention enables methods of treating such inflammatory disorders as arthritic diseases, such as rheumatoid arthritis,
15 osteoarthritis, gouty arthritis, spondylitis; Behcet disease; sepsis, septic shock, endotoxic shock, gram negative sepsis, gram positive sepsis, and toxic shock syndrome; multiple organ injury syndrome secondary to septicemia, trauma, or hemorrhage; ophthalmic disorders such as allergic conjunctivitis, vernal conjunctivitis, uveitis, and thyroid-associated ophthalmopathy; eosinophilic
20 granuloma; pulmonary or respiratory disorders such as asthma, chronic bronchitis, allergic rhinitis, ARDS, chronic pulmonary inflammatory disease (e.g., chronic obstructive pulmonary disease), silicosis, pulmonary sarcoidosis, pleurisy, alveolitis, vasculitis, pneumonia, bronchiectasis, and pulmonary oxygen toxicity; reperfusion injury of the myocardium, brain, or extremities; fibrosis such as cystic fibrosis; keloid
25 formation or scar tissue formation; atherosclerosis; autoimmune diseases such as systemic lupus erythematosus (SLE), autoimmune thyroiditis, multiple sclerosis, some forms of diabetes, and Reynaud's syndrome; and transplant rejection disorders such as GVHD and allograft rejection; chronic glomerulonephritis; inflammatory bowel diseases such as Crohn's disease, ulcerative colitis and necrotizing enterocolitis;
30 inflammatory dermatoses such as contact dermatitis, atopic dermatitis, psoriasis, or urticaria; fever and myalgias due to infection; central or peripheral nervous system

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inflammatory disorders such as meningitis, encephalitis, and brain or spinal cord injury due to minor trauma; Sjögren's syndrome; diseases involving leukocyte diapedesis; alcoholic hepatitis; bacterial pneumonia; antigen-antibody complex mediated diseases; hypovolemic shock; Type I diabetes mellitus; acute and delayed hypersensitivity; disease states due to leukocyte dyscrasia and metastasis; thermal injury; granulocyte transfusion associated syndromes; and cytokine-induced toxicity.

The tank2 polynucleotides provided by the invention also enable therapeutic applications of these polynucleotides in treating the diseases and disorders described herein whose etiology involves TANK2 expression or activity. For example, a tank2 antisense molecule may provide the basis for treatment of various abnormal conditions related to excessive or undesirable levels of poly(ADP-ribose) polymerase activity. Alternatively, polynucleotide sequences encoding TANK2 may provide the basis for the treatment of various abnormal conditions related to deficiency of poly(ADP-ribose) polymerase activity. Polynucleotides having specificity for one or both of tank2-long and tank2-short may have particular utility in certain diseases.

Expression vectors derived from retroviruses, adenovirus, herpes, or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of recombinant tank2 sense or antisense molecules to the targeted cell population. Methods that are well known to those skilled in the art can be used to construct recombinant vectors containing tank2. See, for example, the techniques described in Sambrook et al., *supra*, and Ausubel et al., *supra*. Alternatively, recombinant tank2 can be delivered to target cells in liposomes.

The cDNA sequence, and/or its regulatory elements, enables researchers to use a tank2 polynucleotide as a tool in sense [Yousoufian and Lodish, *Mol Cell Biol* 13:98-104 (1993)] or antisense [Eguchi et al., *Annu Rev Biochem* 60:631-52 (1991)] investigations of gene function. Oligonucleotides, designed from the cDNA or control sequences obtained from the genomic DNA, can be used *in vitro* or *in vivo* to inhibit expression. Such technology is now well known in the art, and sense or antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions. Again, tank2-long- or tank2-short-specific sequences may have distinct utilities depending on which form of tank2 is of interest.

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Additionally, TANK2 expression can be modulated by transfecting a cell or tissue with expression vectors that express high levels of a tank2 polynucleotide fragment in conditions where it would be preferable to block a biological activity of TANK2. Such constructs can flood cells with untranslatable sense or antisense sequences. Even in the absence of integration into the DNA, such vectors may continue to transcribe RNA molecules until all copies of the vector are disabled by endogenous nucleases. Such transient expression may be accomplished using a non-replicating vector or a vector incorporating appropriate replication elements.

Methods for introducing vectors into cells or tissue include those methods discussed herein. In addition, several of these transformation or transfection methods are equally suitable for *ex vivo* therapy. Furthermore, the tank2 polynucleotide sequences disclosed herein may be used in molecular biology techniques that have not yet been developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including but not limited to such properties as the triplet genetic code and specific base pair interactions.

Pharmaceutical Compositions

The present invention further relates to pharmaceutical compositions that comprise a chemical or biological compound ("agent") that is active as a modulator of TANK2 expression or activity and a biocompatible pharmaceutical carrier, adjuvant, or vehicle. The active agent in the pharmaceutical compositions may be selected from among all or portions of tank2 polynucleotide sequences, tank2 antisense molecules, TANK2 polypeptides, protein, peptide, or organic modulators of TANK2 bioactivity, such as inhibitors, antagonists (including antibodies) or agonists. Preferably, the agent is active in treating a medical condition that is mediated by or characterized by TANK2 expression or activity. The composition can include the agent as the only active moiety or in combination with other nucleotide sequences, polypeptides, drugs, or hormones mixed with excipient(s) or other pharmaceutically acceptable carriers.

Techniques for formulation and administration of pharmaceutical compositions may be found in *Remington's Pharmaceutical Sciences*, 18th Ed., Mack Publishing Co., Easton, PA (1990). The pharmaceutical compositions of the present

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invention may be manufactured using any conventional method, e.g., mixing, dissolving, granulating, dragée-making, levigating, emulsifying, encapsulating, entrapping, melt-spinning, spray-drying, or lyophilizing processes. However, the optimal pharmaceutical formulation will be determined by one of skill in the art depending on the route of administration and the desired dosage. Such formulations may influence the physical state, stability, rate of *in vivo* release, and rate of *in vivo* clearance of the administered agent. Depending on the condition being treated, these pharmaceutical compositions may be formulated and administered systemically or locally.

The pharmaceutical compositions may be administered to the subject by any conventional method, including parenteral and enteral techniques. Parenteral administration modalities include those in which the composition is administered by a route other than through the gastrointestinal tract, for example, intravenous, intraarterial, intraperitoneal, intramedullary, intramuscular, intraarticular, intrathecal, and intraventricular injections. Enteral administration modalities include, for example, oral (including buccal and sublingual) and rectal administration. Transepithelial administration modalities include, for example, transmucosal administration and transdermal administration. Transmucosal administration includes, for example, enteral administration as well as nasal, inhalation, and deep lung administration; vaginal administration; and rectal administration. Transdermal administration includes passive or active transdermal or transcutaneous modalities, including, for example, patches and iontophoresis devices, as well as topical application of pastes, salves, or ointments. Surgical techniques include implantation of depot (reservoir) compositions, osmotic pumps, and the like. A preferred route of administration for treatment of inflammation would be local or topical delivery for localized inflammation such as arthritis, and intravenous delivery for reperfusion injury or for systemic conditions such as septicemia.

The pharmaceutical compositions are formulated to contain suitable pharmaceutically acceptable carriers, and may optionally comprise excipients and auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. The administration modality will generally determine the

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nature of the carrier. For example, formulations for parenteral administration may comprise aqueous solutions of the active compounds in water-soluble form. Carriers suitable for parenteral administration can be selected from among saline, buffered saline, dextrose, water, and other physiologically compatible solutions. Preferred carriers for parenteral administration are physiologically compatible buffers such as Hank's solution, Ringer's solutions, or physiologically buffered saline. For tissue or cellular administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. For preparations comprising proteins, the formulation may include stabilizing materials, such as polyols (e.g., sucrose) and/or surfactants (e.g., nonionic surfactants), and the like.

Alternatively, formulations for parenteral use may comprise suspensions of the active compounds prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, and synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Emulsions, e.g., oil-in-water and water-in-oil dispersions, can also be used, optionally stabilized by an emulsifying agent or dispersant (surface-active materials; surfactants). Liposomes containing the active agent may also be employed for parenteral administration. Aqueous polymers that provide pH-sensitive solubilization and/or sustained release of the active agent may also be used as coatings or matrix structures, e.g., methacrylic polymers such as the Eudragit® series available from Röhm America Inc. (Piscataway, NJ).

Alternatively, the pharmaceutical compositions comprising the agent in dosages suitable for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art. The preparations formulated for oral administration may be in the form of tablets, pills, capsules, cachets, dragées, lozenges, liquids, gels, syrups, slurries, suspensions, or powders. To illustrate,

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pharmaceutical preparations for oral use can be obtained by combining the active compounds with a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries if desired, to obtain tablets or dragée cores. Note that oral formulations may employ liquid carriers similar in type to those described for parenteral use, e.g., buffered aqueous solutions, suspensions, and the like.

Preferred oral formulations include tablets, dragées, and gelatin capsules.

These preparations may contain one or excipients, which include, without limitation:

- a) diluents such as sugars, including lactose, dextrose, sucrose, mannitol, or sorbitol;
- b) binders such as magnesium aluminum silicate, starch from corn, wheat, rice, potato, etc.;
- c) cellulose materials such as methyl cellulose, hydroxypropylmethyl cellulose, and sodium carboxymethyl cellulose, polyvinyl pyrrolidone, gums such as gum arabic and gum tragacanth, and proteins such as gelatin and collagen;
- d) disintegrating or solubilizing agents such as cross-linked polyvinyl pyrrolidone, starches, agar, alginic acid or a salt thereof such as sodium alginate, or effervescent compositions;
- e) lubricants such as silica, talc, stearic acid or its magnesium or calcium salt, and polyethylene glycol;
- f) flavorants, and sweeteners;
- g) colorants or pigments, e.g., to identify the product or to characterize the quantity (dosage) of active compound; and
- h) other ingredients such as preservatives, stabilizers, swelling agents, emulsifying agents, solution promoters, salts for regulating osmotic pressure, and buffers.

Gelatin capsules include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating such as glycerol or sorbitol. Push-fit capsules can contain the active ingredient(s) mixed with fillers, binders, lubricants, and/or stabilizers, etc. In soft capsules, the active compounds may be dissolved or

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suspended in suitable fluids, such as fatty oils, liquid paraffin, or liquid polyethylene glycol with or without stabilizers.

Dragée cores can be provided with suitable coatings such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures.

The pharmaceutical composition may be provided as a salt of the active agent, which can be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents that are the corresponding free base forms.

To be effective therapeutically in modulating central nervous system targets, the agents used in the methods of the invention should readily penetrate the blood brain barrier when peripherally administered. Compounds that cannot penetrate the blood brain barrier, however, can still be effectively administered by an intravenous route.

As noted above, the characteristics of the agent itself and the formulation of the agent can influence the physical state, stability, rate of *in vivo* release, and rate of *in vivo* clearance of the administered agent. Such pharmacokinetic and pharmacodynamic information can be collected through pre-clinical *in vitro* and *in vivo* studies, later confirmed in humans during the course of clinical trials. Thus, for any compound used in the method of the invention, a therapeutically effective dose can be estimated initially from biochemical and/or cell-based assays. Then, dosage can be formulated in animal models to achieve a desirable circulating concentration range that modulates TANK2 expression or activity. As human studies are conducted, further information will emerge regarding the appropriate dosage levels and duration of treatment for various diseases and conditions.

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the "therapeutic index," which is typically expressed as the ratio

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LD₅₀/ED₅₀. Compounds that exhibit large therapeutic indices are preferred. The data obtained from such cell culture assays and additional animal studies can be used in formulating a range of dosage for human use. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity.

For the method of the invention, any effective administration regimen regulating the timing and sequence of doses may be used. Doses of the agent preferably include pharmaceutical dosage units comprising an effective amount of the agent. As used herein, "effective amount" refers to an amount sufficient to modulate TANK2 expression or activity and/or derive a measurable change in a physiological parameter of the subject through administration of one or more of the pharmaceutical dosage units.

Exemplary dosage levels for a human subject are of the order of from about 0.001 milligram of active agent per kilogram body weight (mg/kg) to about 100 mg/kg. Typically, dosage units of the active agent comprise from about 0.01 mg to about 10,000 mg, preferably from about 0.1 mg to about 1,000 mg, depending upon the indication, route of administration, etc. Depending on the route of administration, a suitable dose may be calculated according to body weight, body surface area, or organ size. The final dosage regimen will be determined by the attending physician in view of good medical practice, considering various factors that modify the action of drugs, e.g., the agent's specific activity, the severity of the disease state, the responsiveness of the patient, the age, condition, body weight, sex, and diet of the patient, the severity of any infection, etc. Additional factors that may be taken into account include time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Further refinement of the dosage appropriate for treatment involving any of the formulations mentioned herein is done routinely by the skilled practitioner without undue experimentation, especially in light of the dosage information and assays disclosed, as well as the pharmacokinetic data observed in human clinical trials. Appropriate dosages may be ascertained through use of established assays for determining concentration of the agent in a body fluid or other sample together with dose response data.

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The frequency of dosing will depend on the pharmacokinetic parameters of the agent and the route of administration. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect.

Accordingly, the pharmaceutical compositions can be administered in a single dose,
5 multiple discrete doses, continuous infusion, sustained release depots, or combinations thereof, as required to maintain desired minimum level of the agent.

Short-acting pharmaceutical compositions (i.e., short half-life) can be administered once a day or more than once a day (e.g., two, three, or four times a day). Long acting pharmaceutical compositions might be administered every 3 to 4 days, every week, or
10 once every two weeks. Pumps, such as subcutaneous, intraperitoneal, or subdural pumps, may be preferred for continuous infusion.

Compositions comprising a compound of the invention formulated in a pharmaceutical acceptable carrier may be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition. Conditions indicated on the label
15 may include treatment of inflammatory disorders, cancer, nervous tissue injury, etc. Kits are also contemplated, wherein the kit comprises a dosage form of a pharmaceutical composition and a package insert containing instructions for use of the composition in treatment of a medical condition.

The following Examples are provided to further aid in understanding the
20 invention. The particular materials and conditions employed are intended to exemplify particular aspects of the invention and should not be construed to limit the reasonable scope thereof.

The Examples presuppose an understanding of conventional methods well-known to those persons having ordinary skill in the art to which the examples pertain,
25 e.g., the construction of vectors and plasmids, the insertion of genes encoding polypeptides into such vectors and plasmids, or the introduction of vectors and plasmids into host cells. Such methods are described in detail in numerous publications including, for example, Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press (1989), Ausubel et al.
30 (Eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc. (1994); and

Ausubel et al. (Eds.), *Short Protocols in Molecular Biology*, 4th ed., John Wiley & Sons, Inc. (1999).

EXAMPLE 1

5 Identification of an EST Related to Human Tankyrase1 and Isolation of a Tankyrase2 Polynucleotide

Using the nucleotide sequence of human tankyrase1 (SEQ ID NO:3) [Smith et al. (1998), *supra*], a search of the National Center for Biotechnology Information
10 (NCBI) Expressed Sequence Tags (EST) database was performed to identify novel genes that are homologous to tankyrase1. The EST database provides 5' and/or 3' nucleotide sequences for cDNA clones from a variety of tissue sources. The NCBI BLASTn program [Altschul et al., *Nucleic Acids Res* 25:3389-402 (1997)] was used to compare the nucleotide query sequence of human tankyrase1 against a nucleotide
15 sequence database and to identify DNA sequences in the EST sequence database that have significant homology to human tankyrase1. This BLASTn search identified two EST sequences of interest: AA307492 (SEQ ID NO:5) cloned from a human colon carcinoma cell line designated HCC, and H17748 (SEQ ID NO:7), cloned from human brain.

20 A comparison of the AA307492 and tankyrase1 polynucleotides revealed that a region consisting of nucleotides 307 to 432 (nt 307-432) of AA307492 (SEQ ID NO:5) shared significant homology with a region consisting of nt 3313-3438 of tankyrase1 (SEQ ID NO:3); 105 of 126 nucleotides were the same; 83% identity). Nucleotides 307-432 of AA307492 were translated and the predicted protein (SEQ ID
25 NO:6) was compared with tankyrase1 protein (amino acids 1105 to 1146 of SEQ ID NO:4). The proteins were found to be the same at 36 of 42 amino acid positions (86% identity). A comparison of the H17748 and tankyrase1 polynucleotides revealed that nt 3-356 of H17748 (SEQ ID NO:7) shared significant homology with nt 3544-3897 of tankyrase1 (SEQ ID NO:3; 280 of 354 nucleotides were identical; 79% identity).
30 When nt 3-356 of H17748 was translated and the predicted protein (SEQ ID NO:8) was compared with the corresponding region of tankyrase1 (aa 1182-1299 of SEQ ID NO:4), the proteins were found to be the same at 111 of 118 amino acid positions

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(94% identity). The putative amino acid sequences of AA307492 and H17748 are homologous to, but distinct from, tankyrase1 protein, indicating that they represented protein products translated from a novel tankyrase gene or genes.

AA307492 and H17748 were used in a search of the GenBank® database using the NCBI UniGene® program in order to identify other EST sequences originating from the same gene(s). The UniGene® program assembles GenBank sequences into a non-redundant set of gene-oriented clusters, with each cluster containing a group of sequences from the same gene. The UniGene® search of the human GenBank® database with AA307492 did not identify any other human EST sequences clustering in the same gene region as AA307492. By contrast, the UniGene® search of the human GenBank database with H17748 identified sixteen human EST sequences belonging in the same gene cluster as H17748, as follows: AA305587 (SEQ ID NO:9), AA371079 (SEQ ID NO:10), AA970617 (SEQ ID NO:11), AI247608 (SEQ ID NO:12), H11505 (SEQ ID NO:13), H11865 (SEQ ID NO:14), H17635 (SEQ ID NO:15), N29528 (SEQ ID NO:16), N57467 (SEQ ID NO:17), R06902 (SEQ ID NO:18), R06946 (SEQ ID NO:19), R14158 (SEQ ID NO:20), R33944 (SEQ ID NO:21), R63031 (SEQ ID NO:22), R63337 (SEQ ID NO:23), and T17118 (SEQ ID NO:24). EST H17748 and EST H17635 contained sequence from opposite ends of the same clone, designated 50806. EST H11505 and EST H11865 contained sequence from opposite ends of the same clone, designated 47912. EST R06902 and EST R06946 contained sequence from opposite ends of the same clone, designated 126654. *E. coli* strains harboring cDNA clones 50806, 47912, and 126654 were purchased from the American Type Culture Collection (ATCC, Rockville, MD), which maintains and makes publicly available deposits of ESTs identified and sequenced by I.M.A.G.E. (Lawrence Livermore National Laboratory, Livermore, CA). The three clones were sequenced as follows:

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Clone 50806 was sequenced in its entirety on both strands using primers that hybridized to the vector DNA (SEQ ID NOs:25-26), and primers designed to hybridize to the human cDNA (SEQ ID NOs:27-34).

	M13 Forward	TGTAACGACGGCCAGT	(SEQ ID NO:25)
5	M13 Reverse	GGAAACAGCTATGACCATG	(SEQ ID NO:26)
	NT-7	TTTGCCGGGTAACCTTGG	(SEQ ID NO:27)
	NT-8	CCAAGGTTACCCGGCAAA	(SEQ ID NO:28)
	NT-9	GTAGGCCAGTGTAATG	(SEQ ID NO:29)
	NT-10	CATTTACACTGGGCCTAC	(SEQ ID NO:30)
10	NT-11	GAGTAAGTTGCAGGGCATGT	(SEQ ID NO:31)
	NT-12	ACATGCCCTGCAACTTACTC	(SEQ ID NO:32)
	NT-13	GAATCACCGCAGTTACTAAA	(SEQ ID NO:33)
	NT-14	TTTAGTAACTGCGGTGATTC	(SEQ ID NO:34)

Clone 47912 was sequenced in its entirety on both strands using primers that hybridized to the vector DNA (SEQ ID NOs:25-26, *supra*), and primers designed to hybridize to the human cDNA (SEQ ID NOs:27-34, *supra*, and SEQ ID NOs:35-37).

	NT-15	GGCCTGAAGGTATGGTCGAT	(SEQ ID NO:35)
	NT-16	ATCGACCATACCTTCAGGCC	(SEQ ID NO:36)
	NT-18	TGAGGGCATTACAGTTTGTT	(SEQ ID NO:37)

Clone 126654 was sequenced in its entirety on both strands using primers that hybridized to the vector DNA: M13 Forward (SEQ ID NO:25, *supra*) and T7 Promoter (SEQ ID NO:38), and primers designed to hybridize to the human cDNA (SEQ ID NOs:27-30, *supra*, and SEQ ID NOs:39-40).

	T7 Promoter	TAATACGAACTCACTATAGGG	(SEQ ID NO:38)
25	NT-5	ATACACTCACCGGAGAAA	(SEQ ID NO:39)
	NT-6	TTTCTCCGGTGAGTGTAT	(SEQ ID NO:40)

Upon sequencing, 50806, 47912, and 126654 were found to be consistent with the sequences reported in the EST database. The polynucleotide sequences for 50806, 47912, and 126654 are set out in SEQ ID NOs:41, 43, and 45, respectively. The deduced amino acid sequences for 50806, 47912, and 126654 are set out in SEQ ID NOs:42, 44, and 46, respectively. The sequences of 50806 and 47912 indicated that

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the clones were identical, and only 50806 was considered further. 50806 and 126654 contain overlapping nucleotide sequence, but 126654 was 63 base pairs longer at the 5' end, while 50806 was approximately 400 base pairs longer at the 3' end.

50806 was determined to have an open reading (ORF) beginning at nucleotide position 1, a potential intron sequence at nt 358-1138, a stop codon beginning at nt 1999, and a potential poly A tail 474 base pairs 3' to the stop codon. When nt 1-357 of 50806 were compared with nt 3538-3897 of tankyrase1, 283 of 357 nucleotides were the same (79% identical). When 50806 was translated from nt 1-357 and the resultant protein was compared with tankyrase1 (aa 1181-1299), the proteins were the same at 116 of 120 amino acid positions (97% identity).

A putative intron was identified in 50806, consisting of nt 358-1138, which may have been an artifact of cDNA cloning. DNA sequences preceding the putative intron (AG) and at the 3' end of the putative intron (CAG) showed high resemblance to the consensus sequence for exon/intron/exon junctions [Lewin, *GENES IV*, Oxford University Press: New York (1997), at p. 88]. The most common sequence at the 3' end of an exon is AG, and at the 3' end of an intron is CAG. To determine if an intron is included in the 50806 sequence, PCR analysis of genomic DNA is used to verify this prediction.

A comparison of 50806 with tankyrase1 showed that a small region consisting of nt 1139-1198 of 50806 was significantly homologous with nt 3896-3957 of tankyrase1 (40 of 60 nucleotides were the same; 67% identity). When 50806 was translated from nt 1139-1198 and the resultant protein was compared with tankyrase1 (aa 1300 to 1319), the proteins were the same at 14 of 20 amino acid positions (70% identity).

126654 was determined to have an ORF beginning at nucleotide position 1, a stop codon beginning at position 481, and a potential poly A tail 81 base pairs 3' of the stop codon. Comparison of 126654 with tankyrase1 showed that a region consisting of nt 1-480 of 126654 shared significant homology with nt 3478-3957 of tankyrase1 (367 of 481 nucleotides identical; 76% identity). When this region of 126654 was translated and the resultant protein compared with the corresponding region of the tankyrase1 protein (i.e., aa 1160-1319), the proteins were the same at

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149 of 160 amino acid positions (97% identity). It is possible that either of the putative poly A tails of 50806 and 126654 were artifacts of cDNA cloning or that 50806 and 126654 represented a population of mRNA that use different polyadenylation sites. 50806 had a stretch of 8 A residues 81 base pairs 3' to the stop codon, indicating that the putative poly A tail of 126654 was most likely a cloning artifact.

Alignment of AA307492 and 126654 with human tankyrase1 using the Sequencher™ program (Gene Codes Corporation, Ann Arbor, MI) suggested that AA307492 was upstream of 126654, and that 11 nucleotides separated AA307492 and 126654. To confirm that AA307492 and 126654 represented polynucleotide sequence from the same gene, a primer (SEQ ID NO:47) corresponding to the sense strand of AA307492 and a primer (SEQ ID NO:48) corresponding to the antisense strand of 126654 were synthesized for use in a polymerase chain reaction (PCR) with human Marathon®-Ready spleen and testis cDNA (Clontech) as the template.

AA307492 sense CTCCGGACAACAAGGTCTTAACC (SEQ ID NO:47)
126654 antisense CCACCTATGTACGCATGCC (SEQ ID NO:48)

The PCR reaction contained 2.5 µL human spleen Marathon®-Ready cDNA, 2.5 µL human testis Marathon-Ready cDNA, 250 nM each primer, 0.25 mM dNTPs, 1X PCR buffer, 1.8 mM MgCl₂, and 5 Units of Taq polymerase (Perkin Elmer). The reaction was performed in a GeneAmp® PCR System 9700 machine (hereinafter "GeneAmp® PCR System 9700"; PE Applied Biosystems, Norwalk CT) and first heated at 94°C for 2 min, followed by 35 cycles of 94°C for 30 sec, 55°C for 30 sec, and 72°C for 30 sec, and ended with 7 min at 72°C. The PCR fragment was isolated using gel electrophoresis and a QIAquick® Gel Extraction Kit (hereinafter "QIAquick® kit"; Qiagen, Valencia, CA), according to the manufacturer's instructions. The PCR fragment was directly cloned into pCR®2.1-TOPO® vector (Invitrogen, Carlsbad, CA), according to the manufacturer's instructions. The PCR fragment was sequenced with primers that hybridized to the vector DNA (SEQ ID NOs:25 and 26, *supra*), and the sequence of the AA307492/126654 PCR fragment is set out in SEQ ID NO:49.

The sequence confirmed that AA307492 was upstream of 126654 and that these two

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ESTs were separated by 11 nucleotides, and that AA307492 and 126654 were sequences from a novel gene, designated tankyrase2.

To identify the full-length tankyrase2 gene, a probe was generated from 126654 and used to screen a cDNA library using procedures routinely practiced in the art. 126654 was digested with *Xho*I and *Bgl*II, and an approximately 260 nucleotide fragment designated NT-5' was isolated using gel electrophoresis and the QIAquick® kit. NT-5' was labeled with ³²P with a Random Primed DNA Labeling Kit (Boehringer Mannheim/Roche Molecular Biochemicals, Indianapolis, IN) according to the manufacturer's instructions and used to screen 10⁶ cDNAs from a human fetal brain library (Stratagene). Hybridization with labeled probe was performed overnight at 65°C in buffer containing: 3X SSC, 0.1% sarkosyl, 20 mM sodium phosphate, pH 6.8, 10X Denhardt's solution, and 50 µg/mL salmon sperm DNA. The filters were washed at 65°C in buffer containing 2X SSC and 0.1% SDS prior to autoradiography. Forty-six positives were obtained with the NT-5' probe, of which fifteen were first characterized with respect to strength of hybridization with NT-5'. Restriction digest mapping and partial sequencing led to the selection of two clones, designated FB2B.1 and FB2D.1, for further characterization.

FB2B.1 was sequenced in its entirety on both strands with primers that hybridized to the vector DNA, including T7 promoter (SEQ ID NO:38, *supra*) and T3 promoter (SEQ ID NO:50), and primers designed to anneal to the cDNA sequence (SEQ ID NOs:51-69).

T3 promoter	ATTTAACCCTCACTAAAGGG	(SEQ ID NO:50)
2B.1 F1	AAAGGCTCCCATCGGCAAAT	(SEQ ID NO:51)
2B.1 F2	GTTGAGGGCATTACAGTTTG	(SEQ ID NO:52)
25 2B.1 F3	AAAACGTAGAGGCCACTGCT	(SEQ ID NO:53)
2B.1 F4	TGGTGTAGACTGACGCCCTT	(SEQ ID NO:54)
2B.1 F5	TCCGGTGAGTGTATCTTTCC	(SEQ ID NO:55)
2B.1 F6	CTCCTTTGTCTTGGGCATTC	(SEQ ID NO:56)
2B.1 F9	ATCTGCTCTGCCCTCTTGTT	(SEQ ID NO:57)
30 2B.1 F10	GGGTATCGCGGCAATTACA	(SEQ ID NO:58)
2B.1 F11	AACAAGAGGGCAGAGCAGAT	(SEQ ID NO:59)

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	2B.1 F12	TGCCCCATCTCAACTAATAC	(SEQ ID NO:60)
	2B.1 R2	GTAATGCCCTCAACAGAACT	(SEQ ID NO:61)
	2B.1 R3	GGCGTCAGTCTACACCACTT	(SEQ ID NO:62)
	2B.1 R4	TAAATTGCCCCGCGATACCCA	(SEQ ID NO:63)
5	2B.1 R5	CACTCAGTCACTGGTAGGCC	(SEQ ID NO:64)
	2B.1 R6	ATCTGCTCTGCCCTCTTGTT	(SEQ ID NO:65)
	2B.1 R7	TAGTTGAGATGGGGCACAAG	(SEQ ID NO:66)
	2B.1 R8	AAACGTAGAGGCCACTGCTG	(SEQ ID NO:67)
	2B.1 R9	CGGGTAACCTTGGGAAAGTC	(SEQ ID NO:68)
10	2B.1&2D.1	GGGCTTTACTGCTTTACAGA	(SEQ ID NO:69)

FB2D.1 was sequenced in its entirety on both strands with primers that hybridized to the vector DNA (SEQ ID NOs:38 and 50, *supra*) and primers designed to anneal to the cDNA sequence, including 2B.1&2D.1 (SEQ ID NO:69) and SEQ ID NOs:70-87.

15	2D.1 F1	GTAAGGGCTGCTGACAGTGA	(SEQ ID NO:70)
	2D.1 F2	TTACTCCAGCAGAGGGCACT	(SEQ ID NO:71)
	2D.1 F3	CTGACGCCCTTCAATGTCTC	(SEQ ID NO:72)
	2D.1 F4	GGTACTAAGGCCACAATTCA	(SEQ ID NO:73)
	2D.1 F5	GGGTATCGCGGCAATTTACA	(SEQ ID NO:74)
20	2D.1 F6	GTTGAGGGCATTACAGTTTG	(SEQ ID NO:75)
	2D.1 F7	TAACAAGAGGGCAGAGCAGA	(SEQ ID NO:76)
	2D.1 F8	AGTTCTGTTGAGGGCATTAC	(SEQ ID NO:77)
	2D.1 F9	GGCCTACCACTGACTGAGTG	(SEQ ID NO:78)
	2D.1 F10	GGGCTAGAGGACCTGAAGAG	(SEQ ID NO:79)
25	2D.1 R2	AGTGCCCTCTGCTGGAGTAA	(SEQ ID NO:80)
	2D.1 R3	GGCGTCAGTCTACACCACTT	(SEQ ID NO:81)
	2D.1 R4	TGAATTGTGGCCTTAGTACC	(SEQ ID NO:82)
	2D.1 R5	ATGCCCAAGACAAAGGAGGA	(SEQ ID NO:83)
	2D.1 R6	GTAATGCCCTCAACAGAACT	(SEQ ID NO:84)
30	2D.1 R7	ATCTGCTCTGCCCTCTTGTT	(SEQ ID NO:85)
	2D.1 R8	CGGGTAACCTTGGGAAAGTC	(SEQ ID NO:86)

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2D.1 R9 CCGGACAACAAGGTCTTAAC (SEQ ID NO:87).

The polynucleotide sequences for FB2B.1 and FB2D.1 are set out in SEQ ID NOs:88 and 90, respectively, and the deduced amino acid sequences of FB2B.1 and FB2D.1 are set out in SEQ ID NOs:89 and 91, respectively.

5 The nucleotide and amino acid sequences of FB2B.1 and tankyrase1 were compared to determine the degree of relatedness between the sequences. A region consisting of nt 4-279 of FB2B.1 (SEQ ID NO:88) was found to have significant identity with nt 1624-1899 of tankyrase1 (SEQ ID NO:3), wherein 203 of 276 nucleotides were identical (73% identity). Nucleotides 402-1254 of FB2B.1 showed
10 significant identity with nt 2022-2874 of tankyrase1, wherein 630 of 853 nucleotides were identical (73% identity). Furthermore, nt 1507-2338 of FB2B.1 showed homology to nt 3112-3943 of tankyrase1, wherein 634 of 832 nucleotides were identical (76% identity). FB2B.1 was determined to have an ORF beginning at nucleotide position 1, a stop codon beginning at position 2353, approximately 1 kb of
15 3' untranslated sequence, but no apparent poly A tail. A translation of nt 1-2352 of FB2B.1 showed that a region consisting of the predicted amino acid sequence (SEQ ID NO:89) was homologous to a corresponding region of tankyrase1 (aa 540-1327 of SEQ ID NO:4). In this region, the proteins were identical at 623 of 777 amino acid positions (80% identity).

20 A similar comparison of FB2D.1 was made with tankyrase1. In this case, a region consisting of nt 6-197 of FB2D.1 (SEQ ID NO:90) was significantly related to nt 1708-1899 of tankyrase1, wherein 137 of 192 nucleotides were identical (71% identity). Nucleotides 320-1172 of FB2D.1 were found to share significant homology with corresponding nt 2022-2874 of tankyrase1, wherein 630 of 853 nucleotides were
25 identical (73% identity). Nucleotides 1425-2256 of FB2D.1 showed significant homology with nt 3112-3943 of tankyrase1, wherein 634 of 832 nucleotides were identical (76% identity). FB2D.1 was determined to have an ORF beginning at nucleotide position 3, a stop codon beginning at position 2271, approximately 1.5 kb of 3' untranslated sequence, but no apparent poly A tail. When FB2D.1 was
30 translated (SEQ ID NO:91), a domain predicted by the nt 3-2270 showed homology to

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aa 569-1327 of tankyrase1 (SEQ ID NO:4). Here, the proteins were the same at 602 of 749 amino acid positions (80% identity).

FB2B.1 and FB2D.1 were aligned using Sequencher™. FB2B.1 and FB2D.1 contained overlapping polynucleotide sequence, but FB2B.1 was longer at the 5' end by 82 base pairs, and FB2D.1 was longer at the 3' end by approximately 0.5 kb. The nucleotide sequences of FB2B.1 and FB2D.1 were identical in the regions nt 83-2971 of FB2B.1 and nt 1-2889 of FB2D.1. However, the remaining 382 nucleotides of FB2B.1 and 910 nucleotides of FB2D.1 did not align. It is possible that FB2B.1 and FB2D.1 were random primed from different positions in the 3' untranslated region and/or that this misalignment was the result of the presence of a cloning artifact in one or both of the clones. Since FB2B.1 and FB2D.1 did not appear to have poly A tails, the poly A tails of ESTs 50806 and 126654 were most likely cloning artifacts, and the real poly A tail of tankyrase2 was most likely greater than 0.5 kb from the stop codon. A consensus polynucleotide sequence, designated 2B.1/2D.1, was developed from the alignment of FB2B.1 and FB2D.1, and is set out in SEQ ID NO:92. 2B.1/2D.1 contained nt 1-2971 of FB2B.1 and nt 1-2889 of FB2D.1.

Alignment of FB2B.1 and FB2D.1 with tankyrase1 using Sequencher™ suggested that neither FB2B.1 nor FB2D.1 represented a full-length gene, and that nucleotide sequence was missing from the 5' end of tankyrase2. Thus, FB2B.1 was digested with *EcoRI* and *SphI*, and an approximately 466 bp nucleotide fragment located at the immediate 5' end of FB2B.1 (nt 49-515 of SEQ ID NO:88) was isolated using gel electrophoresis and the QIAquick® kit. This fragment was labeled with ³²P with a Random Primed DNA Labeling Kit and used as a probe (designated NT-37/38) to screen 10⁶ cDNA clones of the fetal brain library (Stratagene) using the conditions and procedures used in the first screening. Fourteen positives were obtained with the NT-37/38 probe, one of which (designated 30B.2A) also hybridized with the NT-5' probe, but which had not been chosen for further characterization at that time. Restriction mapping and partial sequencing led to the selection of 30B.2A for further characterization.

The region of 30B.2A upstream of clone FB2B.1 was sequenced with primers that hybridized to the vector DNA (SEQ ID NOs:38 and 50, *supra*) and primers

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designed to anneal to the cDNA sequence, including 2B.1 F4 (SEQ ID NO:54, *supra*) and SEQ ID NOs:93-97).

30B.2A #1	GGGCGGAAAGACGTAGTTGA	(SEQ ID NO:93)
30B.2A #2	GCGGCTGTTCACCTTCTCAG	(SEQ ID NO:94)
5 30B.2A #5	ACGCAAGTGATGGCAGAAAG	(SEQ ID NO:95)
30B.2A #6	TCACTTGCGTGGCAGTTGAC	(SEQ ID NO:96)
30B.2A #7	GCGGCAGGTTTGTAGATGAC	(SEQ ID NO:97)

The partial polynucleotide sequence of 30B.2A is set out in SEQ ID NO:98, and the partial deduced amino acid sequence is set out in SEQ ID NO:99. Comparison of 30B.2A with the nucleotide sequence of tankyrase1 indicated that significant homology occurred in the region consisting of nt 167-1435 of 30B.2A which corresponded with nt 631-1899 of tankyrase1. In this region, 953 of the 1269 nucleotides were the same (75% identity). 30B.2A was determined to have an ORF beginning at nucleotide position 2. Significant amino acid sequence identity was observed between a 385 amino acid sequence predicted for 30B.2A (based on nt 2-1156) and the corresponding region of tankyrase1 (aa 160-539). In this region, the protein sequences were the same at 319 of 385 amino acid positions (83% identity).

2B.1/2D.1 and 30B.2A were aligned using Sequencher™. 30B.2A 2A contained 1.157 kb of novel sequence before it began overlapping with the 5' end of 2B.1/2D.1, and began overlapping with 2B.1/2D.1 at position 1158. A consensus polynucleotide sequence, designated 2B.1/2D.1/30B.2A, was developed from the alignment of 2B.1/2D.1 and 30B.2A, and is set out in SEQ ID NO:100.

2B.1/2D.1/30B.2A contained nt 1-1157 of 30B.2 and nt 1-2971 of 2B.1/2D.1. The predicted amino acid sequence encoded by nt 2-3508 of SEQ ID NO:100 is set forth as SEQ ID NO:101. The nucleotide sequence of the TANK2-encoding region is set forth as SEQ ID NO:1, and the corresponding TANK2 polypeptide sequence is set forth as SEQ ID NO:2.

EXAMPLE 2Cloning of 5' End of Tankyrase2

Alignment of 30B.2A with tankyrase1 using the Sequencer™ program suggested that 5' sequence was still lacking from the tankyrase2 gene. To clone the 5' end of human tankyrase2, 5' RACE analysis was performed using a Marathon®-Ready human spleen cDNA library (Clontech) as the template. A primer (NT-Marathon; SEQ ID NO:102) corresponding to the antisense strand of 2B.1/2D.1/30B.2A polynucleotide sequence (nt 337-367 of SEQ ID NO:100) was synthesized for use in a polymerase chain reaction (PCR) with the AP1 primer (Clontech; SEQ ID NO:103) that was designed to anneal to the Marathon® cDNA Adapters ligated to the ends of the cDNAs in the library.

NT-Marathon GAGCATTGGGGTCTGCACCATGTCGCAAAAGG
(SEQ ID NO:102)

15 AP1 CCATCCTAATACGACTCACTATAGGGC (SEQ ID NO:103)

The PCR reaction contained 5 µL human spleen Marathon®-Ready cDNA, 0.20 µM each primer, 0.20 mM dNTPs, 1X Clontech GC 2 PCR buffer, Clontech GC-Melt buffer (0, 0.5, 1.0, or 1.5 M), and 1 µL of Clontech Advantage®-GC 2 polymerase mix. The reactions were performed in a GeneAmp® PCR System 9700 with the following four steps: 1) 1 cycle at 94°C for 1 min; 2) 5 cycles of 94°C for 30 sec and 72°C for 30 sec; 3) 5 cycles of 94°C for 30 sec and 70°C for 30 sec; and 4) 25 cycles of 94°C for 30 sec and 60°C for 30 sec. The reactions were then continued in the GeneAmp® PCR System 9700 under the following conditions: 1) 1 cycle at 94°C for 1 min; 2) 5 cycles of 94°C for 30 sec, and 72°C for 3 min; 3) 5 cycles of 94°C for 30 sec and 70°C for 3 min; and 4) 25 cycles of 94°C for 30 sec and 60°C for 3 min. The PCR fragments were isolated using gel electrophoresis and a QIAquick® kit as directed. The PCR fragments were directly cloned into the pCR®2.1-TOPO® vector, as directed. Because *Taq* polymerase has an error rate of 8.0×10^{-6} mutation/ base pair (Cline et al., *Nucleic Acids Res* 24:3546-51), four clones isolated from four separate PCR reactions were sequenced and compared to eliminate the possibility of *Taq* polymerase-induced errors in the 5' RACE sequences. The four 5' RACE clones

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were sequenced with the M13 forward and M13 reverse primers (SEQ ID NOs:25 and 26) that hybridize to the vector DNA. The four individual nucleotide sequences were compiled into a consensus nucleotide sequence designated 5'-RACE tank2 that is set out in SEQ ID NO:104, and the deduced amino acid sequence is set out in SEQ ID NO:105. In the consensus nucleotide sequence of 5'-RACE tank2, every base pair was present at the corresponding position in at least three of the four unique clones used to compile the consensus sequence. 5'-RACE tank2 and tankyrase were aligned using the Sequencher™ program. When nt 1-279 of 5'-RACE tank2 (SEQ ID NO:104) were compared with tankyrase no significant similarity was found. 5'-RACE tank2 was determined to have an ORF beginning at nucleotide position 2. When nt 2-277 of 5'-RACE tank2 was translated and the resultant protein was compared with tankyrase, no significant similarity was found.

5'-RACE tank2 and 2B.1/2D.1/30B.2A were aligned using the Sequencher™ program. 5'-RACE tank2 contained 279 bp of novel sequence before it began overlapping with the 5' end of FB2B.1/2D.1/30B.2A, and began overlapping with 2B.1/2D.1/30B.2A at position 280. A consensus polynucleotide sequence designated 2B.1/2D.1/30B.2A/5'-RACE, was developed from the alignment of 5'-RACE tank2 and 2B.1/2D.1/30B.2A and is set out in SEQ ID NO:106. 2B.1/2D.1/30B.2A/5'-RACE contained nt 1-279 of 5'-RACE tank2 and nt 1-4140 of 2B.1/2D.1/30B.2A. The deduced putative amino acid sequence of 2B.1/2D.1/30B.2A/5'-RACE is set out in SEQ ID NO:107.

The presence of a continuous ORF in the 5'-RACE tank sequence suggested that 5' sequence was still lacking from the tankyrase2 gene. Further attempts to obtain additional 5' sequence of tankyrase2 using 5' RACE analysis were unsuccessful. The NCBI BLASTn program was used to compare the nucleotide query sequence of FB2B.1/2D.1/30B.2A against a nucleotide sequence tag database (a non-redundant database of GenBank®+EMBL+DDBJ STS Divisions). This BLASTn search identified a STS tag sequence designated stWI-16054 (GenBank® Accession No. G24639; SEQ ID NO:108). When nt 3608-3985 of 2B.1/2D.1/30B.2A was compared with the antisense complement nt 8-397 of stWI-16054, 361 of 378 nucleotides were the same (96% identical). The Sanger Centre (Cambridge, UK)

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Human Genome Clone Search program (<http://www.sanger.ac.uk/cgi-bin/humace/searcher.cgi>) was used to identify BAC clones containing stWI-16054. BAC clone bA329B8 was identified as containing the STS tag stWI-16054. BAC clone bA329B8 originates from the genomic RPCI-11.2 male white blood cell library (Pieter deJong, Roswell Park Cancer Institute, Buffalo, NY) and was purchased from Research Genetics, Inc. (Huntsville, AL). A Large Construct Kit (Qiagen) was used to isolate bA329B8 DNA, which was used as a template in inverse PCR amplification reactions [Ochman et al., "Amplification of Flanking Sequences by Inverse PCR," pp. 219-27 in *PCR Protocols: A Guide to Methods and Applications* (Innis et al., eds.), Academic Press, San Diego, CA (1990)]. The inverse PCR technique allows for the amplification of unknown DNA sequence flanking a region of known sequence. Briefly, template DNA is digested with a restriction enzyme (preferably, one that recognizes a four or five base pair consensus site), followed by circularization of the restriction fragments. Circularized fragments are used as a template in a PCR reaction with two primers designed to anneal to the known flanking sequence but pointed in opposite directions. One microgram (1 µg) of bA329B8 was digested in a 20 µL reaction containing 1X appropriate reaction buffer and 10 units of one of the following restriction enzymes: *RsaI* (Promega, Madison, WI), *BfaI* (New England Biolabs, Beverly, MA), or *Tru9I* (Promega). The restriction digests were incubated for one hour at 37°C (*RsaI* and *BfaI*) or 65°C (*Tru9I*). The *RsaI* and *BfaI* digests were heated at 68°C for 20 minutes to inactivate the restriction enzymes. A QIAquick® kit was used to inactivate the restriction enzyme in the *Tru9I* digest. Ligation reactions contained the following: 20 µL of the *Tru9I*, *RsaI*, or *BfaI* reactions, 448 µL distilled water, 50 µL 10X reaction buffer, and 2 µL T4 DNA ligase (5U/µL; Boehringer Mannheim, Indianapolis, IN). Ligations were incubated overnight at 15°C. The DNAs in the ligation reactions were then precipitated by adding 129.26 µL 7 M ammonium acetate and 2.3 mL 95% ethanol. The DNAs were pelleted, washed with 75% ethanol, resuspended in 15 µL distilled water, and used as templates in PCR amplification reactions. A primer (5-Inv-1; SEQ ID NO:109) corresponding to the sense strand of 5'-RACE tank2 (nt 423-443 of SEQ ID NO:104) and a primer (3-Inv-

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1; SEQ ID NO:110) corresponding to the antisense strand of 5'-RACE tank2 (nt 364-383 of SEQ ID NO:104) were synthesized for use in PCR amplification reactions.

5-Inv-1 CGCCTGAGAAGGTGAACAGCC (SEQ ID NO:109)

3-Inv-1 ACGCCTCGAACAGCTCTCGG (SEQ ID NO:110)

5 The PCR reactions (final reaction volume of 20 μ L) contained 5 μ L of the *Tru9I*, *RsaI*, or *BfaI* DNA template, 0.20 μ M each primer, 0.20 mM dNTPs, 1X Clontech GC 2 PCR buffer, 1.0 M Clontech GC-Melt buffer, and 0.4 μ L of Clontech Advantage®-GC 2 polymerase. The reactions were performed in a GeneAmp® PCR System 9700 with the following four steps: 1) 1 cycle at 94°C for 1 minute; 2) 5 cycles of 94°C for 30 seconds and 65°C for 3 minutes and 30 seconds; 3) 5 cycles of 94°C for 30 seconds and 60°C for 3 minutes and 30 seconds; and 4) 25 cycles of 94°C for 30 seconds and 58°C for 3 minutes and 30 seconds. The PCR fragments were isolated using gel electrophoresis and a QIAquick® kit as directed. The PCR fragments were directly cloned into the pCR®2.1-TOPO® vector, as directed. The *Tru9I*, *RsaI*, and *BfaI* clones were sequenced with the M13 primers that hybridize to the vector DNA (SEQ ID NOs:25 and 26) and primers designed to anneal to the cDNA sequence (SEQ ID NOs:109-112).

5-Inv-2 GCGTGGGCGCGGCCATGGGACTG (SEQ ID NO:111)

3-Inv-2 CAGCGCGAATCCGCCGTCCG (SEQ ID NO:112)

20 The *Tru9I*, *RsaI*, and *BfaI* polynucleotide sequences are set out in SEQ ID NOs:113, 115, and 117, respectively. The deduced amino acid sequences of *Tru9I*, *RsaI*, and *BfaI* are set out in SEQ ID NOs:114, 116, and 118, respectively.

Clones *Tru9I* and 5'-RACE tank2 were aligned using the Sequencher™ program. Clone *Tru9I* (SEQ ID NO:113) contained 235 bp of novel sequence before it began overlapping with the 5' end of 5'-RACE tank2 (SEQ ID NO:104), and began overlapping with 5'-RACE tank2 at position 236. When nt 1-235 of clone *Tru9I* were compared with tankyrase no significant similarity was found. Clone *Tru9I* was determined to have an ORF beginning at nucleotide position 3. When clone *Tru9I* was translated from nt 3-236 and the resultant protein was compared with tankyrase no significant similarity was found.

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Clone *RsaI* and 5'-RACE tank2 were aligned using the Sequencher™ program. Clone *RsaI* (SEQ ID NO:115) contained 654 bp of novel sequence before it began overlapping with the 5' end of 5'-RACE tank2 (SEQ ID NO:104), and began overlapping with 5'-RACE tank2 at position 655. When nt 1-654 of clone *RsaI* were compared with tankyrase no significant similarity was found. Clone *RsaI* was determined to have an ORF beginning at nucleotide position 160, with a putative ATG start codon beginning at nucleotide 287. When clone *RsaI* was translated from nt 287-655 and the resultant protein was compared with tankyrase no significant similarity was found.

Clone *BfaI* (SEQ ID NO:117) and 5'-RACE tank2 were aligned using the Sequencher™ program. Clone *BfaI* contained 88 bp of novel sequence before it began overlapping with the 5' end of 5'-RACE tank2 (SEQ ID NO:104), and began overlapping with 5'-RACE tank2 at position 89. When nt 1-88 of clone *BfaI* were compared with tankyrase no significant similarity was found. Clone *BfaI* was determined to have an ORF beginning at nucleotide position 3. When clone *BfaI* was translated from nt 3-89 and the resultant protein compared with tankyrase no significant similarity was found.

To confirm the new polynucleotide sequence obtained from the *Tru9I*, *RsaI*, and *BfaI* clones and to determine if introns are present in the new sequence, PCR amplification of cDNA was performed. A primer (5-RSA-1; SEQ ID NO:119) corresponding to the sense strand of clone *RsaI* (nt 59-84 of SEQ ID NO:115) and a primer (3-Inv-1; SEQ ID NO:110) corresponding to the antisense strand of clone *RsaI* (nt 708-727 of SEQ ID NO:115) were synthesized for use in PCR amplification reactions.

5-RSA-1 GTTCCTCTAATCAATCCTGAGC (SEQ ID NO:119)

Six separate PCR reactions were performed (designated 18, 19, 20, 24, 25, and 26) to aid in the identification of *Taq* polymerase-induced errors as described above. Each 20 µL reaction contained 5 µL of human spleen, placenta, or testis Clontech Marathon®-Ready cDNA DNA template, 0.20 µM each primer, 0.20 mM dNTPs, 1X Clontech GC 2 PCR buffer, 1.0 M Clontech GC-Melt buffer, and 0.4 µL of Clontech Advantage®-GC 2 polymerase. The reactions were performed in a GeneAmp® PCR

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System 9700 with the following four steps: 1) 1 cycle at 94°C for 1 min; 2) 5 cycles of 94°C for 30 sec and 65°C for 2.5 min; 3) 5 cycles of 94°C for 30 sec and 60°C for 2.5 min; and 4) 25 cycles of 94°C for 30 sec and 58°C for 2.5 min. The PCR fragments were isolated using gel electrophoresis and a QIAquick® kit as directed. The PCR fragments were directly cloned into the pCR®2.1-TOPO® vector, as directed. Clones 18, 19, 20, 24, 25, and 26 were sequenced with the M13 primers that hybridized to the vector DNA (SEQ ID NOs:25 and 26) and primers designed to anneal to the cDNA sequence (SEQ ID NOs:112, 120, 121, and 122).

5-RSA-2 GGAAAGAGTAATTGATCAGAGCCATC (SEQ ID NO:120)

10 5-RSA-4 CGCCGAAGCCTCTCGCCTCACATTTCC (SEQ ID NO:121)

3-RSA-4 GGAAATGTGAGGCGAGAGGCTTCGGCG (SEQ ID NO:122)

The polynucleotide sequences of clones 18, 19, 20, 24, 25, and 26 are set out in SEQ ID NOs:123-128, respectively.

Clones 18, 19, 20, 24, 25, 26 and clone *RsaI* were aligned using the Sequencher™ program. The polynucleotide sequence of the cDNA clones confirmed that there were no introns present in the *RsaI* clone sequence. Base pairs 1-596 of clones 18, 19, 20, 24, 25, and 26 were compiled into a consensus nucleotide sequence with bp 59-596 of clone *RsaI* that is designated 5'-RSA/cDNA and is set out in SEQ ID NO:129. The polynucleotide sequence of 5'-RSA/cDNA does not include nucleotide sequence 3' to base pair 597 of clones 18, 19, 20, 24, 25, 26, which is discussed below. The polynucleotide sequence of 5'-RSA/cDNA also does not include bp 1-58 of clone *RsaI*, as this nucleotide sequence was not confirmed in the cDNA clone sequence. In the consensus nucleotide sequence of 5'-RSA/cDNA, every base pair was present at the corresponding position in 6 of the 7 clones, except nucleotide position 47 in which the consensus base pair was present at the corresponding position in 4 of the 7 clones.

The alignment of clones 18, 19, 20, 24, 25, and 26 identified a difference in the nucleotide sequence 3' to base pair 597 (reference position in SEQ ID NOs:123-128). All of the aligned clones contain one copy of a 10 base pair sequence (GAGCTGGCAG; SEQ ID NO:130) located at nt 588-597 (SEQ ID NOs:123-128). Clones 19 and 26 have a second copy of the sequence GAGCTGGCAG repeated

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directly adjacent to the first copy (nt 598-607) (SEQ ID NOs:124 and 128). Clone *RsaI*, clone *Tru9I*, and clone *BfaI* also have two copies of the sequence GAGCTGGCAG directly adjacent to each other (nt 646-665 in clone *RsaI*, (SEQ ID NO:115); nt 227-246 in clone *Tru9I* (SEQ ID NO:113); and nt 80-99 in clone *BfaI* (SEQ ID NO:117)). Clones 18, 20, 24, and 25 do not have the second copy of the sequence GAGCTGGCAG. The presence or absence of the second copy of the sequence GAGCTGGCAG could result from an error in PCR amplification caused by *Taq* polymerase. Direct sequencing of genomic DNA can be used to verify this prediction. The presence or absence of the second copy of the sequence GAGCTGGCAG could also be caused by replication and/or repair proteins present in the bacteria used to propagate the cloned DNA. Direct sequencing of PCR products can be used to verify this prediction. The presence or absence of the second copy of the sequence GAGCTGGCAG could also result from alternative 3'-splice acceptor usage. This possibility seems unlikely since the sequences surrounding the GAGCTGGCAG sequence do not show high resemblance to the consensus sequence for exon/intron/exon borders [Lewin, *supra*]. In addition, clones generated from PCR amplification of genomic DNA have been isolated that contain only one copy of the GAGCTGGCAG sequence (Genomic 1X; SEQ ID NO:131) as well as clones containing two copies of the GAGCTGGCAG sequence (clones *RsaI* (SEQ ID NO:115) *Tru9I* (SEQ ID NO:113) and *BfaI* (SEQ ID NO:117)). The presence or absence of the second copy of the sequence GAGCTGGCAG may also be a polymorphism present in the human population. In this case, expression of a long and short form of the TANK2 protein would be possible, as discussed below.

The presence of two copies of the sequence GAGCTGGCAG produces a long form of the TANK2 protein. Clones 19, 26, *RsaI*, *Tru9I*, and *BfaI* were aligned with 5'-RSA/cDNA and 2B.1/2D.1/30B.2A/5'-RACE using the Sequencher™ program. A consensus polynucleotide sequence designated tankyrase2-long was developed from the alignment and is set out in SEQ ID NO:132. The sequence of tankyrase2-long was determined to have an ORF from nt 103-4386, with the first methionine beginning at nt 229. An in-frame stop codon (beginning at nt 100) was present upstream of the putative initiating methionine. Assuming that this residue is the

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initiating methionine, the ORF of tankyrase2-long encodes a protein of 1385 amino acids (designated TANK2-LONG; SEQ ID NO:133) with a predicted molecular weight of 149,892 Da.

5 The presence of one copy of the sequence GAGCTGGCAG produces a short form of the TANK2 protein. Clones 18, 20, 24, and 25 were aligned with 5'-RSA/cDNA and 2B.1/2D.1/30B.2A/5'-RACE using the Sequencher™ program. A consensus polynucleotide sequence designated tankyrase2-short was developed from the alignment and is set out in SEQ ID NO:134. The sequence of tankyrase2-short was determined to have an ORF from nt 513-4376, with the first methionine
10 beginning at nt 876. An in frame stop codon (beginning at nt 510) was present upstream of the putative initiating methionine. Assuming this residue to be the initiating methionine, the ORF of tankyrase2-short encoded a 1166 amino acid protein (designated TANK2-SHORT; SEQ ID NO:135) with a predicted molecular weight of 126,908 Da. TANK2-SHORT is 219 amino acids shorter at the amino terminal end
15 than TANK2-LONG. The putative initiating methionine of TANK2-SHORT corresponds to a methionine at position 120 of TANK2-LONG. Excluding the first 219 amino acids of TANK2-LONG, TANK2-LONG and TANK2-SHORT are identical.

The tankyrase1 gene (SEQ ID NO:3) encodes a protein TANK1 (SEQ ID
20 NO:4) containing a carboxyl-terminal catalytic domain that has homology to the catalytic domain of human PARP1. The polynucleotide sequence of *parp1* is set out in SEQ ID NO:136, and the amino acid sequence of PARP1 is set out in SEQ ID NO:137. The catalytic domain of TANK1 (aa 1176-1314 of SEQ ID NO:4) is homologous to the catalytic domain of PARP1 (aa 854-1014 of SEQ ID NO:137) and
25 contains PARP catalytic activity (Smith et al., *supra*). Similarly, the putative catalytic domain of TANK2-LONG (aa 1242-1382 of SEQ ID NO:133) and TANK2-SHORT (aa 1023-1161 of SEQ ID NO:135) is highly homologous to the catalytic domain of TANK1 (130 of 139 amino acids are the same; 94% identity).

The central domain of TANK1 contains 24 ankyrin repeats, indicating that
30 TANK1 might belong to the ankyrin family of proteins that bridge integral membrane proteins to the cytoskeleton [Bennett, *J Biol Chem* 267: 8703-6 (1992)]. The ankyrin

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repeat domain of TANK1 (aa 181-1110 of SEQ ID NO:4) is significantly homologous to a central domain of TANK2-LONG (aa 242-1078 of SEQ ID NO:133) and TANK2-SHORT (aa 23-859 of SEQ ID NO:135) (692 of 837 amino acids are the same; 83% identity).

5 Within the ankyrin repeat domain of TANK1 is a binding site for the telomeric repeat binding factor-1 (TRF1) (Smith et al., *supra*) that functions to regulate the length of telomeres [van Steensel and de Lange, *Nature* 385:740-3 (1997)]. The TRF1 binding domain of TANK1 (aa 436-797 of SEQ ID NO:4) is significantly homologous to a region of TANK2-LONG (aa 497-858 of SEQ ID NO:133) and
10 TANK2-SHORT (aa 278-639 of SEQ ID NO:135) (297 of 364 amino acids are the same; 82% identity).

 TANK1 also contains a sterile alpha module (SAM) domain [Smith et al., *supra*] that is thought to be involved in protein-protein interactions [Ponting, *Protein Sci* 4: 1928-30 (1995); Schultz et al., *Protein Sci* 6: 249-53 (1997)]. A region of
15 TANK2-LONG (aa 1089-1154 of SEQ ID NO:133) and TANK2-SHORT (aa 870-935 of SEQ ID NO:135) is homologous to the SAM domain of TANK1 (aa 1023-1088 of SEQ ID NO:4) (50 of 66 amino acids are the same; 76% identity).

 A comparison of several putative functional domains of TANK2 (catalytic domain, ankyrin repeats, TRF-1 binding domain, and SAM domain) with TANK1 is
20 discussed above. The additional amino terminal sequence contained in TANK2-LONG (all residues amino terminal to the ankyrin repeats, i.e., aa 1-241 of SEQ ID NO:133) allows for a comparison with the amino terminus of TANK1. The amino terminus of TANK1 contains homopolymeric runs of histidines, prolines, and serines (HPS domain, i.e., aa 1-180 of SEQ ID NO:4) [Smith et al., *supra*]. The amino
25 terminus of TANK2-LONG does not contain a HPS domain nor is it significantly homologous with the amino terminus of TANK1. The amino terminus of TANK2-LONG is also 61 amino acid residues longer than TANK1 and is composed of 48.1% non-polar residues, 32.4% polar residues, and 19.5% charged residues.

 TANK2-SHORT is 219 amino acid residues shorter than TANK2-LONG and
30 only contains 22 amino acid residues amino terminal to the ankyrin repeats. Interestingly, the *Drosophila melanogaster* tankyrase gene (GenBank® Accession No.

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AF132196; SEQ ID NO:138) encodes a putative protein designated dTANK (SEQ ID NO:139) that only contains 21 amino acid residues amino terminal to its ankyrin repeats. The amino terminal ends of TANK2-SHORT and dTANK are not significantly homologous, although the two proteins do share homology in the other putative functional domains discussed above. The catalytic domain of TANK2-SHORT (aa 1023-1161 of SEQ ID NO:135) is homologous to a region of dTANK (aa 1033-1171 of SEQ ID NO:139) (113 of 139 amino acids are the same; 81% identity). The putative ankyrin repeat domain of TANK2-SHORT (aa 23-859 of SEQ ID NO:135) is significantly homologous to a central domain of dTANK (aa 22-875 SEQ ID NO:139) (545 of 858 amino acids are the same; 64% identity). The putative TRF1 binding domain of TANK2-SHORT (aa 278-639 of SEQ ID NO:135) is significantly homologous to a region of dTANK (aa 277-633 SEQ ID NO:139) (241 of 364 amino acids are the same; 66% identity). The putative SAM domain of TANK2-SHORT (aa 870-935 of SEQ ID NO:135) is significantly homologous to a region of dTANK (aa 886-951 of SEQ ID NO:139) (31 of 66 amino acids are the same; 66% identity).

EXAMPLE 3

Preparation of Antibodies Immunoreactive with TANK2 Polypeptides

The present invention provides for antibodies with specificity for TANK2 polypeptides. Antibodies to TANK2 may be produced by any method known in the art typically including, for example, the immunization of laboratory animals with preparations of purified native TANK2, purified recombinant TANK2, purified recombinant fragments of TANK2, or synthetic peptides derived from the TANK2 predicted amino acid sequence. To maximize the probability of obtaining antibodies with appropriate specificity for TANK2, regions of the polypeptide may be selected for use as an immunogen based upon differences in those regions between TANK1 and TANK2. For example, alignment of TANK1 and TANK2 demonstrates that a region consisting of aa 969-974 of TANK1 (SEQ ID NO:4) is substantially different from the corresponding region (aa 1030-1042) of TANK2-LONG (SEQ ID NO:133). In addition, the amino terminal domains of TANK1 (aa 1-180 of SEQ ID NO:4) and TANK2-LONG (aa 1-241 of SEQ ID NO:133) are substantially different, as discussed

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above. These regions can be expressed as truncated polypeptides in an appropriate expression system for use as immunogen or to test polyclonal or monoclonal antibody preparations. Similar approaches can be applied to other regions of the TANK2 polypeptide. Likewise, synthetic peptides can be made to correspond to various regions of differences and such peptides can be utilized to generate specific polyclonal or monoclonal antibodies by methods known in the art. For examples, see discussions in Harlow et al. (1988), *supra*.

Alignment of TANK1 and TANK2 indicated that a region of TANK2-LONG consisting of aa 1030-1042 (SEQ ID NO:133) was substantially different than the corresponding region of TANK1 (aa 969-974 of SEQ ID NO:4). A peptide, designated ICEC #2, having this TANK2 sequence, was synthesized by AnaSpec Inc. (San Jose, CA) for use as an immunogen in antibody development. Peptide ICEC #2 was conjugated to KLH using Imject® Maleimide Activated Carrier Proteins (Pierce, #77106) following the manufacturer's protocol.

Each of four 6 to 12 week old Balb/c mice were pre-bled on day 0 and immunized by subcutaneous injection of 50 µg per mouse of KLH-ICEC-2 peptide in Freund's complete adjuvant. Subsequent boosts were made on day 21 and 42 in Freund's incomplete adjuvant. Mice were test bled on day 52 and the bleeds were screened by ELISA, using standard methods, on plates coated with KLH-ICEC-2 peptide. Specific antibody was detected using goat anti-mouse IgG(fc) horseradish peroxidase (HRP) conjugate. Mouse #3616 was given pre-fusion boosts on day 118 and 119 with 50 µg KLH-ICEC-2 peptide in PBS. The spleen was removed and fused on day 122.

Splenocytes were fused to NS-1 cells in a ratio of 5:1 by standard methods using polyethylene glycol 1500 (Boehringer Mannheim/Roche Molecular Biochemicals) [Harlow et al. (1988), *supra*]. The fused cells were resuspended in 250 mL RPMI containing 15% FBS, 100 mM sodium hypoxanthine, 0.4 mM aminopterin, 16 mM thymidine (HAT) (Gibco BRL, Rockville, MD), 10 units/mL IL-6 (Boehringer Mannheim/Roche Molecular Biochemicals) and 1.5×10^6 murine thymocytes/mL.

The suspension was dispensed into twelve and a half 96-well flat bottom tissue culture plates (Corning, United Kingdom) at 200 µL/well. Cells in plates were fed on

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days 4, 5, and 6 post fusion by aspirating approximately 100 μ L from each well and adding 100 μ L/well plating medium described above except lacking thymocytes.

Supernatants from the fused cells were screened on day 7-12, initially by ELISA on the immunogen, as described above. To ensure clonality, positive wells
5 chosen from the fusion were subcloned 3 times by limiting dilution, using media lacking aminopterin. Cloning was completed for one fusion, 345C, which remained reactive to the immunizing protein. Isotyping of the antibody was performed by standard ELISA methods, using goat anti-mouse IgG1, IgG2a, IgG2b, and IgG3 HRP conjugates as detecting antibodies. The clone 345C was IgG1.

10 Western analysis was also used to test immunoreactivity of 345C to TANK2. 1×10^7 non-proliferating human PBL cells were pelleted by centrifugation and lysed by addition of 0.5 mL Buffer D [0.1% NP 40, 0.1% TX-100, 100 mM KCl, 20 mM HEPES, pH 7.9, 0.2 mM EDTA, 0.2 mM EGTA, 1.0 mM dithiothreitol (DTT), and protease inhibitor cocktail tablets, (Boehringer Mannheim/Roche Molecular
15 Biochemicals)]. Lysates were sonicated (Sonifier® 250, Branson Ultrasonics Corp., Danbury, CT) at 20% output for 30 seconds and clarified in a 4°C microfuge for 5 min and the pellets discarded. Mouse IgG (2.5 μ g) or 0.5 mL 345C mAb culture supernatant was added to the lysates and they were incubated for 90 min at 4°C. Immune complexes were collected by precipitation with 30 μ L protein G-Agarose
20 slurry (Pierce) with gentle rocking for 30 minutes at 4°C. Pellets were washed 4X in Buffer D, resuspended in 25 μ L 1X SDS Sample buffer [50 mM Tris-HCl, pH 6.8, 2% SDS, 0.1% bromophenol blue, 10% glycerol, and 100 mM DDT], and heated for 5 min at 100°C.

Samples were electrophoresed on 8% Tris-Glycine polyacrylamide gels
25 (Novex, San Diego, CA) at 60 mA for 30 min, as described by the manufacturer. Gels were transferred to Immobilon-P transfer membrane (Millipore, Bedford, MA) using a Bio-Rad (Hercules, CA) semi-dry blotting apparatus at 150 mA for 90 min as described by the manufacturer. Blots were then blocked in TBST buffer (Tris buffered saline, pH 7.5 and 0.5% Tween®) containing 5.0% nonfat dry milk for 20-30
30 min at room temperature. Primary mAb 345C culture supernatant was then added at a 1:2 dilution to TBST containing 1.0% nonfat dry milk and blots were incubated at

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room temperature for 90 min. Following 4 washes with TBST, secondary antibody (goat anti-mouse IgG HRP conjugate, Bio-Rad) was added at a 1/3,000 dilution in TBST containing 1.0% nonfat dry milk and blots were incubated for 30 min at room temperature. Blots were again washed 4X in TBST followed by incubation in ECL detection reagents (Amersham Life Sciences, Uppsala, Sweden) as described by the manufacturer, followed by exposure to X-ray film. Positive signals of approximately the expected size for TANK2-LONG and TANK2-SHORT were obtained. The entire procedure is repeated to obtain more strongly immunoreactive monoclonal antibodies.

10 **EXAMPLE 4**

Analysis of Tank2 Expression by Northern Blot Hybridization

In order to identify cell and tissue types that express tankyrase2 mRNA, Northern blot analysis was performed using commercially prepared multi-tissue Northern blots (Clontech). The DNA probe template was amplified by PCR using a primer (5-Tank2-15; SEQ ID NO:140) corresponding to the sense strand of FB2B.1 polynucleotide sequence (nt 2330-2349 of SEQ ID NO:88) and a primer (3-Tank2-18; SEQ ID NO:141) corresponding to the antisense strand of FB2B.1 polynucleotide sequence (nt 2656-2675 of SEQ ID NO:88).

5-Tank2-15 GGCCTGAAGGTATGGTCGAT (SEQ ID NO:140)

20 3-Tank2-18 TGAGGGCATTACAGTTTGT (SEQ ID NO:141)

The PCR reaction contained 100 ng FB2B.1 cDNA, 0.25 μ M each primer, 0.20 mM dNTPs, 1X PCR buffer, and 1 μ L of Clontech Advantage® polymerase mix. The reactions were performed in a GeneAmp® PCR System 9700 with the following steps: 1) 1 cycle at 94°C for 1 min; 2) 30 cycles of 94°C for 30 sec, 60°C for 30 sec, and 72°C for 30 sec; and 3) 1 cycle at 72°C for 7 min. The PCR fragment (designated Tank2-Nprobe; SEQ ID NO:142) was isolated using gel electrophoresis and a QIAquick® kit as directed. Tank2-Nprobe was labeled with ³²P with a Random Primed DNA Labeling Kit (Boehringer Mannheim/Roche Molecular Biochemicals) as directed and used to probe Clontech multi-tissue Northern blots. Prehybridization with Clontech's ExpressHyb™ DNA Hybridization solution was performed at 68°C for 30 min. Hybridization with labeled probe was performed for 1 hr at 68°C in

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ExpressHyb™. The blots were washed three times at room temperature in buffer containing 2X SSC and 0.05% SDS and then washed two times at 50°C in buffer containing 0.1X SSC and 0.1% SDS prior to autoradiography.

5 The tissue Northern blot contained an approximately 6.3 kb band whose signal was strongest in placenta, PBL, ovary, and spleen and was present in pancreas, kidney, skeletal muscle, liver, lung, brain, heart, colon, small intestine, testis, prostate, and thymus.

EXAMPLE 5

10 Analysis of Tank2 Expression by *in situ* Hybridization

Expression of tankyrase2 was examined in tissue sections by *in situ* hybridization as described below.

Preparation of probes

15 A probe for tankyrase2 *in situ* hybridization was generated using procedures routinely practiced in the art. A primer (5-Tank2-15p; SEQ ID NO:143) corresponding to the sense strand of FB2B.1 polynucleotide sequence (nt 2330-2349 of SEQ ID NO:88) and a primer (3-Tank2-18p; SEQ ID NO:144) corresponding to the antisense strand of FB2B.1 polynucleotide sequence (nt 2656-2675 of SEQ ID
20 NO:88) were synthesized for use in a PCR reaction using FB2B.1 as the template.

5-Tank2-15p GCCGAATTCGGCCTGAAGGTATGGTCGAT

(SEQ ID NO:143)

3-Tank2-18p GCCGAATTCTAGATGAGGGCATTACAGTTTGTT

(SEQ ID NO:144)

25 The PCR reaction contained 100 ng FB2B.1 cDNA, 0.5 μM each primer, 0.25 mM dNTPs, 1X PCR buffer, and 2.5 U of *PfuTurbo*® polymerase mix (Stratagene). The reactions were performed in a GeneAmp® PCR System 9700 with the following steps: 1) 1 cycle at 94°C for 1 min; 2) 25 cycles of 94°C for 30 sec, 55°C for 1 min, and 72°C for 1 min; and 3) 1 cycle at 72°C for 7 min. The PCR fragment was
30 digested with *EcoRI*, isolated using gel electrophoresis and a QIAquick® kit, and subcloned into a Bluescript® vector (Stratagene). The clone, designated Tank2-

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ISprobe, was sequenced with the M13 primers designed to anneal to the vector (SEQ ID NOs:25 and 26) and the sequence is set out in SEQ ID NO:145. Tank2-ISprobe was digested with *XhoI* and transcribed (see below) with T3 polymerase to generate an antisense probe. A sense probe was generated by digesting Tank2-ISprobe with *Bam*HI and transcribing with T7 polymerase.

To compare the tissue expression of tankyrase2 with tankyrase1, a tankyrase1 probe was generated. The tankyrase1 probe corresponds to a region in the 3' untranslated sequence of the tankyrase1 gene. The 3' untranslated sequence of tankyrase1, designated 3-Tank1UT, is set out in SEQ ID NO:146. A primer (5-Tank1-7p; SEQ ID NO:147) corresponding to the sense strand of 3-Tank1UT polynucleotide sequence (nt 407-426 of SEQ ID NO:146) and a primer (3-Tank1-13p; SEQ ID NO:148) corresponding to the antisense strand of 3-Tank1UT polynucleotide sequence (nt 742-767 of SEQ ID NO:146) were synthesized for use in a PCR reaction using 3-Tank1UT as the template.

5-Tank1-7p GCCGAATTCCTTGTTTTGATTTGCCAGA (SEQ ID NO:147)
 3-Tank1-13p GCCGAATTCGGCTTTGACTTCTCTGAATTTAGG
 (SEQ ID NO:148)

The PCR reaction contained 100 ng 3-Tank1UT cDNA, 0.5 μ M each primer, 0.25 mM dNTPs, 1X PCR buffer, and 2.5 U of *PfuTurbo*® polymerase mix (Stratagene).

The reactions were performed in a GeneAmp® PCR System 9700 with the following steps: 1) 1 cycle at 94°C for 1 min; 2) 30 cycles of 94°C for 30 sec, 55°C for 1 min, and 72°C for 1 min; and 3) 1 cycle at 72°C for 7 min. The PCR fragment was digested with *Eco*RI, isolated using gel electrophoresis and a QIAquick® kit, and subcloned into a Bluescript® vector (Stratagene). The clone, designated Tank1-ISprobe, was sequenced with the M13 primers (SEQ ID NOs:25 and 26) and the sequence is set out in SEQ ID NO:149. Tank1-ISprobe was digested with *Bam*HI and transcribed with T7 polymerase to generate an antisense probe. A sense probe was generated by digesting Tank1-ISprobe with *Xho*I and transcribing with T3 polymerase.

The Tank1-IS probe and Tank2-ISprobe were transcribed using a RNA Transcription kit (Stratagene) in a reaction containing 5 μ L of 5X transcription buffer,

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30 mM DTT, 0.8mM each ATP, CTP, GTP, 40 U RNase Block II, 12.5 U T3 or T7 polymerase, 300 ng linearized plasmid template, and 50 μ Ci 35 S-UTP (greater than 1000 Ci/mmol, Amersham, Arlington Heights, IL). The mixture was incubated at 37°C for 1 hr, after which the template DNA was removed by addition of 1 μ L of RNase-free DNase I (Stratagene) and incubated for 15 min at 37°C. A Quick Spin G50 RNA column (5' \rightarrow 3' Inc., Boulder, CO) was prepared according to the manufacturer's suggested protocol. Twenty-five microliters (25 μ L) of dH₂O was added to the probe and it was placed in the center of the column and the column centrifuged for 4 min at 1100 rpm in a desk top centrifuge. The column flow-through was mixed with 50 μ L dH₂O, 2 μ L of a 10mg/mL tRNA solution, 10 μ L 3 M sodium acetate, and 200 μ L 100% ethanol (VWR, So. Plainfield, NJ) and the resulting mixture was incubated at -20°C overnight. The probe solution was centrifuged for 15 min at 4°C, the supernatant was removed, and the pellet was resuspended in 40 μ L 1X TBE [90 mM Tris-Borate and 2 mM EDTA (pH 8.0)] containing 1 μ L of 0.1 M DTT. The probe was stored at -70°C until the *in situ* hybridization was performed.

Preparation of tissue samples and *in situ* hybridization

Tissues (National Disease Research Interchange, Philadelphia, PA and Cooperative Human Tissue Network, Philadelphia, PA) were sectioned at 6 μ m and placed on Superfrost® Plus slides (VWR). Sections were fixed for 20 min at 4°C in 4% paraformaldehyde (Sigma, St. Louis, MO). The slides were rinsed in three changes of 1X CMF-PBS, dehydrated with three successive washes with 70% ethanol, 95% ethanol, and 100% ethanol, and dried for 30 min at room temperature. The slides were placed in 70% formamide (J.T. Baker, Phillipsburg, NJ) in 2X SSC for 2 min at 70°C, rinsed in 2X SSC at 4°C, dehydrated through 70%, 95%, and 100% ethanol washes, and dried for 30 min at room temperature. Slides were placed in an airtight box containing a piece of filter paper saturated with box buffer containing 50% formamide in 4X SSC. The probes, as described above, were individually prepared by mixing 4 X 10⁵ cpm/ tissue section with 5 μ L of a 10 mg/mL tRNA solution per section and heating the mixture at 95°C for 3 min. Ice-cold rHB2 buffer [10% dextran sulfate (Sigma), 50% formamide, 100 mM DTT (Boehringer

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Mannheim/Roche Molecular Biochemicals), 0.3 M NaCl (Sigma), 20 mM Tris, pH 7.5, 5 mM EDTA (Sigma), and 1X Denhardt's solution (Sigma)] was added to the probe mixture to bring the final volume to 60 μ L/section. The probe solution was then added to the tissue sections. The slides were incubated at 50°C for 12-16 hr.

5 Following hybridization, the slides were washed once in 4X SSC containing 10 mM DTT for 1 hr at room temperature, once in 50% deionized formamide, 1X SSC, and 1 mM DTT for 40 min at 60°C, once in 2X SSC for 30 min at room temperature, and once in 0.1X SSC for 30 min at room temperature. The sections were dehydrated through 70%, 95%, and 100% ethanol washes and air dried for 30 min. The slides
10 were dipped in Kodak (Rochester, NY) NTB2 nuclear emulsion at 45°C for 3 hr at room temperature in the dark and stored in the dark at 4°C with desiccant until time of development.

The slides were rinsed in dH₂O and stained with hematoxylin and eosin by transfer of the slides through a series of the following steps: 5 min in
15 formaldehyde/alcohol (100 mL formaldehyde, 900 mL 80% ethanol); three rinses in water for a total of 2 min; 5 min in 0.75% Harris hematoxylin (Sigma); three rinses in water for a total of 2 min; one dip in 1% HCl/50% ethanol; one rinse in water; four dips in 1% lithium carbonate; 10 min in tap water; 2 min in 0.5% eosin (Sigma); three rinses in water for a total of 2 min; 2 min in 70% ethanol; three 1 min rinses in 95%
20 ethanol; two 1 min rinses in 100% ethanol; and two 2 min rinses in xylene. Slides were mounted with cytooseal 60 (Stephens Scientific, Riverdale, NJ).

The signals obtained with the antisense tankyrase1 or antisense tankyrase2 probes were compared to the control signals obtained by the respective sense probes and any signal specific to the antisense tankyrase1 or antisense tankyrase2 probe was
25 assumed to represent tankyrase1 or tankyrase2 expression, respectively. Both tankyrase1 and tankyrase2 signal was detected in most areas of the human testis, including the spermatogonia and spermatocytes. Tankyrase1 signal was detected in the red pulp of the human spleen while tankyrase2 signal was detected in the white pulp of the human spleen. The probes for tankyrase1 and tankyrase2 are used to
30 detect expression in other tissues in a similar manner. Tankyrase1 signal was detected uniformly in mouse embryo, with the highest signal present in the skin. Tankyrase2

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signal was also detected uniformly in mouse embryo, with the highest signal present in the mesenchymal areas and in the brain.

EXAMPLE 6

5 Identification of a Tankyrase2 Binding Partner

As described above, TANK1 interacts with the telomere-specific DNA binding protein TRF1 [Smith et al., (1998), *supra*]. The polynucleotide sequence of TRF1 is set out in SEQ ID NO:150, and the amino acid sequence of TRF1 is set out in SEQ ID NO:151. The yeast two-hybrid system [Hollenburg et al., *Mol Cell Biol* 10 15:3813-22 (1995)] was used to determine if TANK2 also interacts with TRF1. In this yeast two-hybrid system, the yeast strain L40 has been engineered to contain multiple LexA binding sites upstream of the *HIS3* and beta-galactosidase genes. Interaction of one protein fused to LexA (created in the BTM116 vector) with a second protein fused to the VP16 activation domain (created in the VP16 vector) 15 results in the expression of *HIS3*, allowing yeast growth in media lacking histidine. Interaction of the two proteins also results in the expression of the beta-galactosidase gene, which can be measured in a colorimetric assay [Breedon and Nasmyth, *Cold Spring Harbor Symp Quant Biol* 643-650 (1985)]

The TANK1 binding domain of TRF1, here designated TRF1-TankBD, has 20 been mapped to an amino terminal region of TRF1. TRF1-TankBD was amplified by PCR using a primer (5-TRF1; SEQ ID NO:152) corresponding to the sense strand of TRF1 polynucleotide sequence (nt 1-24 of SEQ ID NO:150) and a primer (3-TRF1; SEQ ID NO:153) corresponding to the antisense strand of TRF1 polynucleotide sequence (nt 184-201 of SEQ ID NO:150).

25 5-TRF1 GCCCCGGGGATCCTCATGGCGGAGGATGTTTCCTCAGCG
(SEQ ID NO:152)
3-TRF1 TCCCGGGGATCCTCACACCAGGCCCGCGTCCTC
(SEQ ID NO:153)

The PCR reaction contained 5 µL Clontech human testis Marathon®-Ready cDNA, 30 0.20 µM each primer, 0.20 mM dNTPs, 1X PCR buffer, and 1 µL of Clontech Advantage® polymerase mix. The reactions were performed in a GeneAmp® PCR

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System 9700 with the following steps: 1) 1 cycle at 94°C for 1 min; 2) 30 cycles of 94°C for 30 sec, 60°C for 30 sec, and 72°C for 30 sec; and 3) 1 cycle at 72°C for 7 min. The PCR fragment was digested with *Bam*HI, isolated using gel electrophoresis and a QIAquick® kit as directed, and subcloned into the BTM116 vector. TRF1-TankBD was sequenced with the M13 reverse primer designed to anneal to the vector (SEQ ID NO:26) and a primer designed to anneal to the cDNA sequence (SEQ ID NO:153). The polynucleotide sequence of TRF1-TankBD is set out in SEQ ID NO:154 and the amino acid sequence is set out in SEQ ID NO:155.

As described above, the TRF1 binding domain of TANK1 is very homologous to a region of TANK2 comprised of aa 497-858 of SEQ ID NO:133. The polynucleotide region corresponding to this domain of TANK2, designated Tank2-TRF1BD, was amplified in a PCR reaction with a primer (5-T2/TRF1BD; SEQ ID NO:156) corresponding to the sense strand of the tank2 polynucleotide sequence (nt 1717-1742 of SEQ ID NO:132) and a primer (3-T2/TRF1BD; SEQ ID NO:157) corresponding to the antisense strand of the tank2 polynucleotide sequence (nt 2765-2805 of SEQ ID NO:132).

5-T2/TRF1BD CGCAGGATCCCCTTCACTCCTCTTCATGAGGCAGCTTC
(SEQ ID NO:156)

3-T2/TRF1BD GGATCCGCTAAATATCTGTATCTCCATCTTTAACAA
GATCCAAAGGAG (SEQ ID NO:157)

The PCR reaction contained 5 µL Clontech human testis Marathon®-Ready cDNA, 0.5 µM each primer, 0.25 mM dNTPs, 1X PCR buffer, and 2.5 U of *PfuTurbo*® polymerase mix (Stratagene). The reactions were performed in a GeneAmp® PCR System 9700 with the following steps: 1) 1 cycle at 94°C for 1 min; 2) 30 cycles of 94°C for 30 sec, 55°C for 2 min, and 72°C for 2 min; and 3) 1 cycle at 72°C for 7 min. The PCR fragment was isolated using gel electrophoresis and a QIAquick® kit as directed, and subcloned into the pCR-BluntII™-TOPO® vector (Invitrogen). Tank2-TRF1BD was digested from the pCR-BluntII™-TOPO® with *Bam*HI, and subcloned into the VP16 vector. The Tank2-TRF1BD clone was sequenced with primers designed to adhere to the vector sequence: M13 forward (SEQ ID NO:25) and 009 (SEQ ID NO:158).

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009 GCCGACTTCGAGTTTGAGCAG (SEQ ID NO:158)

The polynucleotide sequence is set out in SEQ ID NO:159 and the amino acid sequence is set out in SEQ ID NO:160.

5 Co-transformation of L40 with the TRF1-TankBD and Tank2-TRF1BD plasmids indicated that like TANK1, TANK2 binds to TRF1.

EXAMPLE 7

Measurement of TANK2 Biological Activity

Construction of Expression Plasmids

10 The primary structure of the tankyrase2 polypeptide suggests that TANK2, like TANK1, will have poly(ADP-ribose) polymerase activity. The PARP activity of TANK2, or some substructure thereof, can be measured by the ability of that component to incorporate the ADP-ribose unit from NAD into polymers of ADP-ribose coupled to a protein substrate. For example, TANK1 adds polymers of ADP-ribose to the TRF-1 protein in molecular assays [Smith et al., *supra*]. TANK2 is
15 expected to also perform this function and/or to ADP-ribosylate another substrate or substrates. The demonstration of such activity on a given substrate is readily accomplished by the skilled artisan [see, for example, Smith et al., *supra*].

20 Structural differences in TANK1 and TANK2 suggest the possibility that TANK2 may have different protein substrate specificity than does TANK1. As demonstrated by the observation that TANK1 binds to TRF-1 and poly ADP-ribosylates TRF-1, it is anticipated that protein substrates of TANK2 can be identified by their ability to bind to TANK2. Additional substrates that bind TANK2 can be identified by a number of methods as described elsewhere in this application.

25 A fusion protein, designated PARP1A/TANK2B, containing aa 1-662 of PARP1 (SEQ ID NO:137) fused upstream of aa 996-1385 of TANK2 (SEQ ID NO:133) was used in the measurement of TANK2 poly(ADP-ribose) polymerase activity. PARP1A/TANK2B contained the DNA binding domain (aa 1-373 of SEQ ID NO:137) and automodification domain (aa 373-525 of SEQ ID NO:137) of PARP1
30 and the putative catalytic domain of TANK2 (aa 1242-1382 of SEQ ID NO:133).

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The PARP1A piece of the fusion protein was amplified by PCR using a primer (Sal-PARP1; SEQ ID NO:161) corresponding to the sense strand of *parp1* polynucleotide sequence (nt 1-30 of SEQ ID NO:136) and a primer (revMlu-PARP1; SEQ ID NO:162) corresponding to the antisense strand of *parp1* polynucleotide sequence (nt 1957-1985 of SEQ ID NO:136).

Sal-PARP1 CGTCGACCCATGGCGGAGTCTTCGGATAAGCTCTATCGA
(SEQ ID NO:161)

revMlu-PARP1
GGAAACGCGTTTGGTGCCAGGATTTACTGTCAGCTTCTT
(SEQ ID NO:162)

The PCR reaction contained 0.5 μ L of human thymus and testis QUICK-Clone™ cDNA (Clontech), 0.25 μ M each primer, 0.20 mM dNTPs, 1X PCR buffer, and 1 μ L of Clontech Advantage® polymerase mix. The reactions were performed in a GeneAmp® (PE Applied Biosystems) with the following steps: 1) 1 cycle at 94°C for 1 min; 2) 30 cycles of 94°C for 30 sec, 60°C for 2 min, and 72°C for 2 min; and 3) 1 cycle at 72°C for 7 min. The PCR fragment (designated *parp1A*) was isolated using gel electrophoresis and a QIAquick® kit as directed. *Parp1A* was subcloned into the pTrcHis2™-TOPO® vector (Invitrogen) as directed. *Parp1A* was digested from pTrcHis2™-TOPO® with *SalI* and *MluI*, the fragment isolated using gel electrophoresis and a QIAquick® kit, and saved for further subcloning described below.

The TANK2B piece of the fusion protein was amplified by PCR using a primer (forMlu-TANK2; SEQ ID NO:163) corresponding to the sense strand of *tank2* polynucleotide sequence (nt 3214-3240 of SEQ ID NO:132) and a primer (TANK2-Strep-Not; SEQ ID NO:164) corresponding to the antisense strand of *tank2* polynucleotide sequence (nt 4350-4383 of SEQ ID NO:132).

ForMlu-TANK2
CTTAAACGCGTTGAAGGACAAACACCTTTAGATTTAGTT
(SEQ ID NO:163)

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TANK2-Strep-Not

GTCGAAAGCGGCCGCTTAGCCTCCGAACTGTGGATGCC

TCCACGCTCCATCGACCATACCTTCAGGCCTCATAATCTGG

(SEQ ID NO:164)

- 5 The PCR reaction contained 100 ng 2B.1 cDNA, 0.25 μ M each primer, 0.20 mM dNTPs, 1X PCR buffer, and 1 μ L of Clontech Advantage® polymerase mix. The reactions were performed in a GeneAmp® PCR System 9700 with the following steps: 1) 1 cycle at 94°C for 1 min; 2) 30 cycles of 94°C for 30 sec, 60°C for 2 min, and 72°C for 2 min; and 3) 1 cycle at 72°C for 7 min. The PCR fragment (designated
- 10 tank2B) was isolated using gel electrophoresis and a QIAquick® kit as directed. Tank2B was subcloned into the pCDNA3.1/NT-GFP-TOPO® vector (Invitrogen) as directed. Tank2B was digested from pCDNA3.1/NT-GFP-TOPO® with *Mlu*I and *Not*I and subcloned with *Sall*/*Mlu*I digested *parp1A* (see above) into a pFASTBAC vector (Gibco BRL), which had previously been digested with *Sall* and *Not*I. The
- 15 resultant plasmid was designated pFB-PARP1A/TANK2B.

pFB-PARP1A/TANK2B was sequenced with primers designed to anneal to the vector sequence (SEQ ID NOs:165-166) and primers designed to anneal to the cDNA sequence (SEQ ID NOs:55, 60, and 66, *supra*, and SEQ ID NOs:167-176).

Vector Primers

- 20 FastBac for TTTGTTGCCCCAGACTC (SEQ ID NO:165)
FastBac rev TATGTTTCAGGTTTCAGGGGAG (SEQ ID NO:166)

cDNA Primers

- P1 GCGGAAGCTGGAGGAGTGAC (SEQ ID NO:167)
P2 GTCACCTCCTCCAGCTTCCGC (SEQ ID NO:168)
25 P3 AAGCCCTGAAGAAGCAGCTC (SEQ ID NO:169)
P4 GAGCTGCTTCTTCAGGGCTT (SEQ ID NO:170)
P5 CAGACACCCAACCGGAAGGA (SEQ ID NO:171)
P6 TCCTTCCGGTTGGGTGTCTG (SEQ ID NO:172)
P7 TCCGCCTCCACCAAGAGCCT (SEQ ID NO:173)
30 P8 AGGCTCTTGGTGGAGGCGGA (SEQ ID NO:174)
P9 TGGCCTGGTGGACATCGTTA (SEQ ID NO:175)
P10 TAACGATGTCCACCAGGCCA (SEQ ID NO:176)

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The nucleotide sequence of PARP1A/TANK2B is set out in SEQ ID NO:177 and the amino acid sequence of PARP1A/TANK2B is set out in SEQ ID NO:178.

PARP1A/TANK2B consists of the following regions: a HIS tag leader region at aa 1-36; a PARP1 region at aa 37-698; a spacer region at aa 699-700; a TANK2 region at
5 aa 701-1090; and a *Strep*-tag region at aa 1091-1099.

Production of Recombinant Viral Stocks and Protein Purification

PARP1A/TANK2B recombinant viral stock was produced using the FastBac system (Gibco BRL) according to the manufacturer's suggested protocol and protein
10 expression was carried out as follows. Sf9 cells were grown at 27°C in CCM3 medium (Hyclone, Logan, UT) containing 50 U/mL penicillin and 50 µg/mL streptomycin sulfate (Gibco BRL). Exponentially growing cells were infected at a multiplicity of infection of approximately 0.5 virus per cell and incubated for 48 hr. Cells were collected by centrifugation at 1000 X g for 15 min, and the pellets were
15 frozen and stored at -80°C until use.

For protein purification, reagents were obtained from Sigma unless otherwise indicated. Cells were lysed in Lysis buffer [25 mM Tris-HCl, pH 9.0, 50 mM glucose, 10 mM EDTA, 1 mM 2-mercaptoethanol, 1 mM PMSF, 100 µM antipain, and 2 µg/mL aprotinin] by sonication. Igepal CA-630 (final concentration of 0.2%),
20 Tween®-20 (final concentration of 0.2%), and NaCl (final concentration of 0.5 M) were added to the Lysis buffer and the samples were agitated for 30 min at 4°C. The supernatants were collected after centrifugation at 20,000 X g for 20 min at 4°C, at which time they were treated with 1 mg/mL protamine sulfate and allowed to stir for 1 hr at 4°C. The supernatants were collected after centrifugation at 4,000 X g for 20
25 min at 4°C at which time the protein was precipitated with 70% ammonium sulfate. Protein pellets were collected by centrifugation at 20,000 X g for 15 min at 4°C and resuspended in Re-suspension buffer [100 mM Tris-HCl, pH 7.4, 0.5 mM EDTA, 10% glycerol, 1 mM PMSF, and 12 mM 2-mercaptoethanol].

Proteins were first purified via the HIS tag using Talon® Superflow metal
30 affinity resin (Clontech) and eluted with 200 mM imidazole (Clontech) as directed. The protein elutions were next purified using a 3-aminobenzamide Affi-Gel® matrix

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(Bio-Rad Laboratories) prepared as described elsewhere [D'Amours et al., *Anal Biochem* 249:106-8 (1997)]. Proteins were eluted with 10 mM 3-methoxybenzamide in Elution buffer [50 mM Tris-HCl, pH 7.5, 0.3 M NaCl, 10 mM 2-mercaptoethanol, 1 mM PMSF, 100 μ M antipain, and 2 μ g/mL aprotinin]. The proteins were dialyzed
5 4 X in 1 L Dialysis buffer [50 mM Tris-HCl, pH 8.0, 1 mM DTT, 4 mM MgCl_2 , 10 mM EDTA, 1 mM PMSF, and 2 μ g/mL aprotinin]. Glycerol was added to a final concentration of 10% and the proteins were stored at -80°C .

Poly(ADP-ribose) polymerase activity

10 For poly(ADP-ribose) polymerase activity assays, reagents were obtained from Sigma unless otherwise indicated. PARP1A/TANK2B (250 ng) protein was incubated for 10 min at room temperature in Assay buffer (total volume of 20 μ L) [100 mM Tris-HCl, pH 8.0, 10 mM MgCl_2 , 10% glycerol, 1.5 mM DTT (Boehringer Mannheim/Roche Molecular Biochemicals), 2.5 μ M unlabeled NAD^+ , 16.7 μ g/mL *E.*
15 *coli* Strain B DNA, and 0.33 μCi γ -[^{32}P]- NAD^+ (NEN, Boston, MA). Reactions were stopped by boiling in SDS running buffer and separated by SDS-polyacrylamide gel electrophoresis (SDS-PAGE). Autoradiography was used to visualize labeled protein. Addition of poly(ADP-ribose) polymers to protein substrate results in an increase in molecular weight of the protein, and consequently causes the protein to run higher on
20 SDS PAGE. Also, the level of poly(ADP-ribose) polymers added to the protein substrate can vary with each single protein molecule, resulting in labeled proteins with different molecular weights, which appears on the autoradiography film as a ladder or smear [for example, see Smith et al. *Science* 282:2484-7 (1998)]. PARP1A/TANK2B possessed intrinsic poly(ADP-ribose) polymerase activity as shown by its ability
25 produce poly(ADP-ribose) polymers. The PARP1A/TANK2B poly(ADP-ribose) polymerase reaction produced a ladder of labeled protein from approximately 136 kDa to 250 kDa.

All publications and patent documents cited in this specification are incorporated herein by reference for all that they disclose.

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While the present invention has been described with specific reference to certain preferred embodiments for purposes of clarity and understanding, it will be apparent to the skilled artisan that further changes and modifications may be practiced
5 within the scope of the invention as it is defined in the claims set forth below. Accordingly, no limitations should be placed on the invention other than those specifically recited in the claims.

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WHAT IS CLAIMED IS:

1. A purified and isolated tankyrase2 polypeptide.
2. The polypeptide according to Claim 1, comprising the amino acid sequence defined in SEQ ID NO:133.
3. The polypeptide according to Claim 1, comprising the amino acid sequence defined in SEQ ID NO:135.
4. A polynucleotide encoding the polypeptide according to Claim 1.
5. The polynucleotide according to Claim 4, comprising the coding region of the nucleotide sequence defined in SEQ ID NO:132.
6. The polynucleotide according to Claim 4, comprising the coding region of the nucleotide sequence defined in SEQ ID NO:134.
7. A polynucleotide selected from the group consisting of:
 - (a) the polynucleotide according to Claim 4,
 - (b) a polynucleotide complementary to the polynucleotide of (a), and
 - (c) a polynucleotide that hybridizes under moderately stringent hybridization conditions to the polynucleotide of (a) or (b).
8. The polynucleotide according to Claim 7, wherein the polynucleotide is a DNA molecule or an RNA molecule.
9. The polynucleotide according to Claim 8, further comprising a detectable label moiety.

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10. An expression construct, comprising the polynucleotide according to Claim 4.
11. A host cell transformed or transfected with the expression construct according to Claim 10.
12. The polynucleotide according to Claim 4, wherein the polynucleotide is operatively linked to a heterologous promoter.
13. A host cell, comprising the polynucleotide according to Claim 12.
14. A method for producing a tankyrase2 polypeptide, comprising the steps of:
 - a) growing the host cell according to Claim 11 or 13 under conditions appropriate for expression of the polypeptide; and
 - b) isolating the polypeptide from the host cell or the medium in which the host cell is grown.
15. An antibody that is specifically immunoreactive with the polypeptide according to Claim 1.
16. The antibody according to Claim 15, wherein the antibody is selected from the group consisting of monoclonal antibodies, polyclonal antibodies, single chain antibodies (scFv antibodies), chimeric antibodies, bifunctional/bispecific antibodies, humanized antibodies, human antibodies, CDR-grafted antibodies, Fab fragments, Fab' fragments, F(ab')₂ fragments, and Fv fragments.
17. A cell line that produces an antibody according to Claim 15.
18. An anti-idiotypic antibody that is specifically immunoreactive with an antibody according to Claim 15.

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19. A method for identifying a binding partner of a tankyrase2 polypeptide, comprising:

- a) contacting the tankyrase2 polypeptide with a test compound under conditions that permit binding of the tankyrase2 polypeptide and the test compound;
 - b) detecting binding of the test compound and the tankyrase2 polypeptide;
- and
- c) identifying the test compound as a binding partner of the tankyrase2 polypeptide.

20. The method according to Claim 19, wherein said specific binding partner selectively or specifically modulates a biological activity of the tankyrase2 polypeptide.

21. A method for identifying a specific binding partner of a tankyrase2 polynucleotide, comprising:

- a) contacting the tankyrase2 polynucleotide with a test compound under conditions that permit binding of the tankyrase2 polynucleotide and the test compound;
- b) detecting binding of the test compound and the tankyrase2 polynucleotide; and
- c) identifying the test compound as a specific binding partner of the tankyrase2 polynucleotide.

22. The method according to Claim 21, wherein said binding partner selectively or specifically modulates activity of the tankyrase2 polynucleotide.

23. A method of treating an animal having a medical condition mediated by poly(ADP-ribose) polymerase activity, comprising administering to said animal a tankyrase2 inhibitory compound in an amount effective for inhibiting tankyrase2 activity in said animal.

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24. The method according to Claim 23, wherein said medical condition is associated with growth of neoplastic tissue.

25. The method according to Claim 24, wherein said neoplastic tissue is a cancer selected from the group consisting of carcinomas, sarcomas, leukemias, and lymphomas.

26. The method according to Claim 25, wherein said cancer is selected from the group consisting of ACTH-producing tumor, acute lymphocytic leukemia, acute nonlymphocytic leukemia, cancer of the adrenal cortex, bladder cancer, brain cancer, breast cancer, cervical cancer, chronic lymphocytic leukemia, chronic myelocytic leukemia, colorectal cancer, cutaneous T-cell lymphoma, endometrial cancer, esophageal cancer, Ewing's sarcoma, gallbladder cancer, hairy cell leukemia, head and neck cancer, Hodgkin's lymphoma, Kaposi's sarcoma, kidney cancer, liver cancer, lung cancer (small and non-small cell), malignant peritoneal effusion, malignant pleural effusion, melanoma, mesothelioma, multiple myeloma, neuroblastoma, glioma, non-Hodgkin's lymphoma, osteosarcoma, ovarian cancer, ovarian (germ cell) cancer, pancreatic cancer, penile cancer, prostate cancer, retinoblastoma, skin cancer, soft tissue sarcoma, squamous cell carcinomas, stomach cancer, testicular cancer, thyroid cancer, trophoblastic neoplasms, uterine cancer, vaginal cancer, cancer of the vulva, and Wilm's tumor.

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SEQUENCE LISTING

<110> Christenson, Erik
DeMaggio, Anthony J
Goldman, Phyllis S
McElligott, David L

<120> Tankyrase2 Materials and Methods

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Leu His Phe Ala Ala Gly Phe Gly Arg Lys Asp Val Val Glu Tyr Leu
             65             70             75             80

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Leu Gln Asn Gly Ala Asn Val Gln Ala Arg Asp Asp Gly Gly Leu Ile
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cct ctt cat aat gca tgc tct ttt ggt cat gct gaa gta gtc aat ctc 337
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Thr Pro Leu His Glu Ala Ala Ile Lys Gly Lys Ile Asp Val Cys Ile
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Asp Asn Leu Gly Gln Thr Ser Leu His Arg Ala Ala Tyr Cys Gly His	
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Leu Gln Thr Cys Arg Leu Leu Leu Ser Tyr Gly Cys Asp Pro Asn Ile	
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Lys Leu Cys Thr Val Gln Ser Val Asn Cys Arg Asp Ile Glu Gly Arg	
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Gly Gly Leu Val Pro Leu His Asn Ala Cys Ser Tyr Gly His Tyr Glu	
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Val Ala Glu Leu Leu Val Lys His Gly Ala Val Val Asn Val Ala Asp	
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Leu Trp Lys Phe Thr Pro Leu His Glu Ala Ala Ala Lys Gly Lys Tyr	
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gaa att tgc aaa ctt ctg ctg cag cat ggt gca gac cct aca aaa aaa	1873
Glu Ile Cys Lys Leu Leu Leu Gln His Gly Ala Asp Pro Thr Lys Lys	
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aac agg gat gga aat act cct ttg gat ctt gtt aaa gat gga gat aca	1921
Asn Arg Asp Gly Asn Thr Pro Leu Asp Leu Val Lys Asp Gly Asp Thr	
625 630 635 640	
gat att caa gat ctg ctt agg gga gat gca gct ttg cta gat gct gcc	1969
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Lys Lys Gly Cys Leu Ala Arg Val Lys Lys Leu Ser Ser Pro Asp Asn	
660 665 670	
gta aat tgc cgc gat acc caa ggc aga cat tca aca cct tta cat tta	2065
Val Asn Cys Arg Asp Thr Gln Gly Arg His Ser Thr Pro Leu His Leu	
675 680 685	

-4-

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aat gca gca tct tac ggg cat gta gat gta gca gct cta cta ata aag Asn Ala Ala Ser Tyr Gly His Val Asp Val Ala Ala Leu Leu Ile Lys 725 730 735	2209
tat aat gca tgt gtc aat gcc acg gac aaa tgg gct ttc aca cct ttg Tyr Asn Ala Cys Val Asn Ala Thr Asp Lys Trp Ala Phe Thr Pro Leu 740 745 750	2257
cac gaa gca gcc caa aag gga cga aca cag ctt tgt gct ttg ttg cta His Glu Ala Ala Gln Lys Gly Arg Thr Gln Leu Cys Ala Leu Leu Leu 755 760 765	2305
gcc cat gga gct gac ccg act ctt aaa aat cag gaa gga caa aca cct Ala His Gly Ala Asp Pro Thr Leu Lys Asn Gln Glu Gly Gln Thr Pro 770 775 780	2353
tta gat tta gtt tca gca gat gat gtc agc gct ctt ctg aca gca gcc Leu Asp Leu Val Ser Ala Asp Asp Val Ser Ala Leu Leu Thr Ala Ala 785 790 795 800	2401
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cca tat tta act ttg aac acc tct ggt agt gga aca att ctt ata gat Pro Tyr Leu Thr Leu Asn Thr Ser Gly Ser Gly Thr Ile Leu Ile Asp 945 950 955 960	2881

-5-

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agt aca gtt cga gag cac aga gat gga ggt cat gca ggt gga atc ttc 2977
Ser Thr Val Arg Glu His Arg Asp Gly Gly His Ala Gly Gly Ile Phe
                      980                      985                      990

aac aga tac aat att ctc aag att cag aag gtt tgt aac aag aaa cta 3025
Asn Arg Tyr Asn Ile Leu Lys Ile Gln Lys Val Cys Asn Lys Lys Leu
                      995                      1000                      1005

tgg gaa aga tac act cac cgg aga aaa gaa gtt tct gaa gaa aac cac 3073
Trp Glu Arg Tyr Thr His Arg Arg Lys Glu Val Ser Glu Glu Asn His
1010                      1015                      1020

aac cat gcc aat gaa cga atg cta ttt cat ggg tct cct ttt gtg aat 3121
Asn His Ala Asn Glu Arg Met Leu Phe His Gly Ser Pro Phe Val Asn
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Ala Ile Ile His Lys Gly Phe Asp Glu Arg His Ala Tyr Ile Gly Gly
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Met Phe Gly Val Tyr Gly Ile Tyr Phe Ala Glu Asn Ser Ser Lys Ser Asn
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 85 90 95
 Pro Leu His Asn Ala Cys Ser Phe Gly His Ala Glu Val Val Asn Leu
 100 105 110
 Leu Leu Arg His Gly Ala Asp Pro Asn Ala Arg Asp Asn Trp Asn Tyr
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 Thr Pro Leu His Glu Ala Ala Ile Lys Gly Lys Ile Asp Val Cys Ile
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 Val Leu Leu Gln His Gly Ala Glu Pro Thr Ile Arg Asn Thr Asp Gly
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 Arg Thr Ala Leu Asp Leu Ala Asp Pro Ser Ala Lys Ala Val Leu Thr
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 Gly Glu Tyr Lys Lys Asp Glu Leu Leu Glu Ser Ala Arg Ser Gly Asn
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 Glu Glu Lys Met Met Ala Leu Leu Thr Pro Leu Asn Val Asn Cys His
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 Ala Ser Asp Gly Arg Lys Ser Thr Pro Leu His Leu Ala Ala Gly Tyr
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 Asn Arg Val Lys Ile Val Gln Leu Leu Leu Gln His Gly Ala Asp Val
 225 230 235 240
 His Ala Lys Asp Lys Gly Asp Leu Val Pro Leu His Asn Ala Cys Ser
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 Tyr Gly His Tyr Glu Val Thr Glu Leu Leu Val Lys His Gly Ala Cys
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 290 295 300
 Asp Pro Thr Leu Leu Asn Cys His Asn Lys Ser Ala Ile Asp Leu Ala
 305 310 315 320
 Pro Thr Pro Gln Leu Lys Glu Arg Leu Ala Tyr Glu Phe Lys Gly His
 325 330 335
 Ser Leu Leu Gln Ala Ala Arg Glu Ala Asp Val Thr Arg Ile Lys Lys
 340 345 350
 His Leu Ser Leu Glu Met Val Asn Phe Lys His Pro Gln Thr His Glu
 355 360 365
 Thr Ala Leu His Cys Ala Ala Ala Ser Pro Tyr Pro Lys Arg Lys Gln
 370 375 380
 Ile Cys Glu Leu Leu Leu Arg Lys Gly Ala Asn Ile Asn Glu Lys Thr
 385 390 395 400
 Lys Glu Phe Leu Thr Pro Leu His Val Ala Ser Glu Lys Ala His Asn
 405 410 415

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Asp Val Val Glu Val Val Val Lys His Glu Ala Lys Val Asn Ala Leu
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 Asp Asn Leu Gly Gln Thr Ser Leu His Arg Ala Ala Tyr Cys Gly His
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 450 455 460
 Ile Ser Leu Gln Gly Phe Thr Ala Leu Gln Met Gly Asn Glu Asn Val
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 Arg Gln Leu Leu Glu Ala Ala Lys Ala Gly Asp Val Glu Thr Val Lys
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 Lys Leu Cys Thr Val Gln Ser Val Asn Cys Arg Asp Ile Glu Gly Arg
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 Gln Ser Thr Pro Leu His Phe Ala Ala Gly Tyr Asn Arg Val Ser Val
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 Val Glu Tyr Leu Leu Gln His Gly Ala Asp Val His Ala Lys Asp Lys
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 595 600 605
 Glu Ile Cys Lys Leu Leu Leu Gln His Gly Ala Asp Pro Thr Lys Lys
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 625 630 635 640
 Asp Ile Gln Asp Leu Leu Arg Gly Asp Ala Ala Leu Leu Asp Ala Ala
 645 650 655
 Lys Lys Gly Cys Leu Ala Arg Val Lys Lys Leu Ser Ser Pro Asp Asn
 660 665 670
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 675 680 685
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 Ile Thr Gln Phe Val Arg Asn Leu Gly Leu Glu His Leu Met Asp Ile
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 Thr Ala Ser Gly Leu Ala Pro Phe Ala Ser Pro Arg His Gly Leu Ala
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 Cys Thr Val Ala Ala Ala Pro Val Val Pro Ala Val Ser Thr Ser Ser
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Ala Arg Glu Ala Asp Leu Ala Lys Val Lys Lys Thr Leu Ala Leu Glu	
500 505 510	
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Ile Ile Asn Phe Lys Gln Pro Gln Ser His Glu Thr Ala Leu His Cys	
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Ala Val Ala Ser Leu His Pro Lys Arg Lys Gln Val Thr Glu Leu Leu	
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ctt aga aaa gga gca aat gtt aat gaa aaa aat aaa gat ttc atg act	1680
Leu Arg Lys Gly Ala Asn Val Asn Glu Lys Asn Lys Asp Phe Met Thr	
545 550 555 560	
ccc ctg cat gtt gca gcc gaa aga gcc cat aat gat gtc atg gaa gtt	1728
Pro Leu His Val Ala Ala Glu Arg Ala His Asn Asp Val Met Glu Val	
565 570 575	
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Leu His Lys His Gly Ala Lys Met Asn Ala Leu Asp Thr Leu Gly Gln	
580 585 590	
act gct ttg cat aga gcc gcc cta gca ggc cac ctg cag acc tgc cgc	1824
Thr Ala Leu His Arg Ala Ala Leu Ala Gly His Leu Gln Thr Cys Arg	
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Leu Leu Leu Ser Tyr Gly Ser Asp Pro Ser Ile Ile Ser Leu Gln Gly	
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Phe Thr Ala Ala Gln Met Gly Asn Glu Ala Val Gln Gln Ile Leu Ser	
625 630 635 640	
gag agt aca cct ata cgt act tct gat gtt gat tat cga ctc tta gag	1968
Glu Ser Thr Pro Ile Arg Thr Ser Asp Val Asp Tyr Arg Leu Leu Glu	
645 650 655	
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660 665 670	
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Gln Asn Val Asn Cys Arg Asp Leu Glu Gly Arg His Ser Thr Pro Leu	
675 680 685	
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His Phe Ala Ala Gly Tyr Asn Arg Val Ser Val Val Glu Tyr Leu Leu	
690 695 700	
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His His Gly Ala Asp Val His Ala Lys Asp Lys Gly Gly Leu Val Pro	
705 710 715 720	
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Leu His Asn Ala Cys Ser Tyr Gly His Tyr Glu Val Ala Glu Leu Leu	
725 730 735	
gta agg cat ggg gct tct gtc aat gtg gcg gac tta tgg aaa ttt acc	2256
Val Arg His Gly Ala Ser Val Asn Val Ala Asp Leu Trp Lys Phe Thr	
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Pro Leu His Glu Ala Ala Ala Lys Gly Lys Tyr Glu Ile Cys Lys Leu	
755 760 765	
ctt tta aaa cat gga gca gat cca act aaa aag aac aga gat gga aat	2352
Leu Leu Lys His Gly Ala Asp Pro Thr Lys Lys Asn Arg Asp Gly Asn	
770 775 780	
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Thr Pro Leu Asp Leu Val Lys Glu Gly Asp Thr Asp Ile Gln Asp Leu	
785 790 795 800	
ctg aaa ggg gat gct gct ttg ttg gat gct gcc aag aag ggc tgc ctg	2448
Leu Lys Gly Asp Ala Ala Leu Leu Asp Ala Ala Lys Lys Gly Cys Leu	
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gca aga gtg cag aag ctc tgt acc cca gag aat atc aac tgc aga gac	2496
Ala Arg Val Gln Lys Leu Cys Thr Pro Glu Asn Ile Asn Cys Arg Asp	
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acc cag ggc aga aat tca acc cct ctg cac ctg gca gca ggc tat aat	2544
Thr Gln Gly Arg Asn Ser Thr Pro Leu His Leu Ala Ala Gly Tyr Asn	
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aac ctg gaa gta gct gaa tat ctt cta gag cat gga gct gat gtt aat	2592
Asn Leu Glu Val Ala Glu Tyr Leu Leu Glu His Gly Ala Asp Val Asn	
850 855 860	
gcc cag gac aag ggt ggt tta att cct ctt cat aat gcg gca tct tat	2640
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ggg cat gtt gac ata gcg gct tta ttg ata aaa tac aac acg tgt gta	2688
Gly His Val Asp Ile Ala Ala Leu Leu Ile Lys Tyr Asn Thr Cys Val	
885 890 895	
aat gca aca gat aag tgg gcg ttt act ccc ctc cat gaa gca gcc cag	2736
Asn Ala Thr Asp Lys Trp Ala Phe Thr Pro Leu His Glu Ala Ala Gln	
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Lys Gly Arg Thr Gln Leu Cys Ala Leu Leu Leu Ala His Gly Ala Asp	
915 920 925	
ccc acc atg aag aac cag gaa ggc cag acg cct ctg gat ctg gca aca	2832
Pro Thr Met Lys Asn Gln Glu Gly Gln Thr Pro Leu Asp Leu Ala Thr	
930 935 940	
gct gac gat atc aga gct ttg ctg ata gat gcc atg ccc cca gag gcc	2880
Ala Asp Asp Ile Arg Ala Leu Leu Ile Asp Ala Met Pro Pro Glu Ala	
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tta cct acc tgt ttt aaa cct cag gct act gta gtg agt gcc tct ctg	2928
Leu Pro Thr Cys Phe Lys Pro Gln Ala Thr Val Val Ser Ala Ser Leu	
965 970 975	
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Ile Ser Pro Ala Ser Thr Pro Ser Cys Leu Ser Ala Ala Ser Ser Ile	
980 985 990	
gac aac ctc act ggc cct tta gca gag ttg gcc gta gga gga gcc tcc	3024
Asp Asn Leu Thr Gly Pro Leu Ala Glu Leu Ala Val Gly Gly Ala Ser	
995 1000 1005	
aat gca ggg gat ggc gcc gcg gga aca gaa agg aag gaa gga gaa gtt	3072
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gaa cac ctt cgg gat atc ttt gaa aca gaa cag att aca cta gat gtg 3168
 Glu His Leu Arg Asp Ile Phe Glu Thr Glu Gln Ile Thr Leu Asp Val
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ttg gct gat atg ggt cat gaa gag ttg aaa gaa ata ggc atc aat gca 3216
 Leu Ala Asp Met Gly His Glu Glu Leu Lys Glu Ile Gly Ile Asn Ala
 1060 1065 1070

tat ggg cac cgc cac aaa tta atc aaa gga gta gaa aga ctc tta ggt 3264
 Tyr Gly His Arg His Lys Leu Ile Lys Gly Val Glu Arg Leu Leu Gly
 1075 1080 1085

gga caa caa ggc acc aat cct tat ttg act ttt cac tgt gtt aat cag 3312
 Gly Gln Gln Gly Thr Asn Pro Tyr Leu Thr Phe His Cys Val Asn Gln
 1090 1095 1100

gga acg att ttg ctg gat ctt gct cca gaa gat aaa gaa tat cag tca 3360
 Gly Thr Ile Leu Leu Asp Leu Ala Pro Glu Asp Lys Glu Tyr Gln Ser
 1105 1110 1115 1120

gtg gaa gaa gag atg caa agt act att cga gaa cac aga gat ggt ggt 3408
 Val Glu Glu Glu Met Gln Ser Thr Ile Arg Glu His Arg Asp Gly Gly
 1125 1130 1135

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 Asn Ala Gly Gly Ile Phe Asn Arg Tyr Asn Val Ile Arg Ile Gln Lys
 1140 1145 1150

gtt gtc aac aag aag ttg agg gag cgg ttc tgc cac cga cag aag gaa 3504
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 Val Ser Glu Glu Asn His Asn His His Asn Glu Arg Met Leu Phe His
 1170 1175 1180

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 Gly Ser Pro Phe Ile Asn Ala Ile Ile His Lys Gly Phe Asp Glu Arg
 1185 1190 1195 1200

cat gca tac ata gga gga atg ttt ggg gcc ggg att tat ttt gct gaa 3648
 His Ala Tyr Ile Gly Gly Met Phe Gly Ala Gly Ile Tyr Phe Ala Glu
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aac tcc tca aaa agc aac caa tat gtt tat gga att gga gga gga aca 3696
 Asn Ser Ser Lys Ser Asn Gln Tyr Val Tyr Gly Ile Gly Gly Gly Thr
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 Gly Cys Pro Thr His Lys Asp Arg Ser Cys Tyr Ile Cys His Arg Gln
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atg ctc ttc tgt aga gtg acc ctt ggg aaa tcc ttt ctg cag ttt agc 3792
 Met Leu Phe Cys Arg Val Thr Leu Gly Lys Ser Phe Leu Gln Phe Ser
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acc atg aaa atg gcc cac gcg cct cca ggg cac cac tca gtc att ggt 3840
 Thr Met Lys Met Ala His Ala Pro Pro Gly His His Ser Val Ile Gly
 1265 1270 1275 1280

aga ccg agc gtc aat ggg ctg gca tat gct gaa tat gtc atc tac aga 3888
 Arg Pro Ser Val Asn Gly Leu Ala Tyr Ala Glu Tyr Val Ile Tyr Arg
 1285 1290 1295

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 Gly Glu Gln Ala Tyr Pro Glu Tyr Leu Ile Thr Tyr Gln Ile Met Lys
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cca gaa gcc cct tcc cag acc gca aca gcc gca gag cag aag acc tag 3984
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 35 40 45
 Thr Ala Ser Gly Leu Ala Pro Phe Ala Ser Pro Arg His Gly Leu Ala
 50 55 60
 Leu Pro Glu Gly Asp Gly Ser Arg Asp Pro Pro Asp Arg Pro Arg Ser
 65 70 75 80
 Pro Asp Pro Val Asp Gly Thr Ser Cys Cys Ser Thr Thr Ser Thr Ile
 85 90 95
 Cys Thr Val Ala Ala Ala Pro Val Val Pro Ala Val Ser Thr Ser Ser
 100 105 110
 Ala Ala Gly Val Ala Pro Asn Pro Ala Gly Ser Gly Ser Asn Asn Ser
 115 120 125
 Pro Ser Ser Ser Ser Ser Pro Thr Ser Ser Ser Ser Ser Ser Pro Ser
 130 135 140
 Ser Pro Gly Ser Ser Leu Ala Glu Ser Pro Glu Ala Ala Gly Val Ser
 145 150 155 160
 Ser Thr Ala Pro Leu Gly Pro Gly Ala Ala Gly Pro Gly Thr Gly Val
 165 170 175
 Pro Ala Val Ser Gly Ala Leu Arg Glu Leu Leu Glu Ala Cys Arg Asn
 180 185 190
 Gly Asp Val Ser Arg Val Lys Arg Leu Val Asp Ala Ala Asn Val Asn
 195 200 205
 Ala Lys Asp Met Ala Gly Arg Lys Ser Ser Pro Leu His Phe Ala Ala
 210 215 220
 Gly Phe Gly Arg Lys Asp Val Val Glu His Leu Leu Gln Met Gly Ala
 225 230 235 240
 Asn Val His Ala Arg Asp Asp Gly Gly Leu Ile Pro Leu His Asn Ala
 245 250 255
 Cys Ser Phe Gly His Ala Glu Val Val Ser Leu Leu Leu Cys Gln Gly
 260 265 270
 Ala Asp Pro Asn Ala Arg Asp Asn Trp Asn Tyr Thr Pro Leu His Glu
 275 280 285

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Ala Ala Ile Lys Gly Lys Ile Asp Val Cys Ile Val Leu Leu Gln His
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 Gly Ala Asp Pro Asn Ile Arg Asn Thr Asp Gly Lys Ser Ala Leu Asp
 305 310 315 320
 Leu Ala Asp Pro Ser Ala Lys Ala Val Leu Thr Gly Glu Tyr Lys Lys
 325 330 335
 Asp Glu Leu Leu Glu Ala Ala Arg Ser Gly Asn Glu Glu Lys Leu Met
 340 345 350
 Ala Leu Leu Thr Pro Leu Asn Val Asn Cys His Ala Ser Asp Gly Arg
 355 360 365
 Lys Ser Thr Pro Leu His Leu Ala Ala Gly Tyr Asn Arg Val Arg Ile
 370 375 380
 Val Gln Leu Leu Leu Gln His Gly Ala Asp Val His Ala Lys Asp Lys
 385 390 395 400
 Gly Gly Leu Val Pro Leu His Asn Ala Cys Ser Tyr Gly His Tyr Glu
 405 410 415
 Val Thr Glu Leu Leu Leu Lys His Gly Ala Cys Val Asn Ala Met Asp
 420 425 430
 Leu Trp Gln Phe Thr Pro Leu His Glu Ala Ala Ser Lys Asn Arg Val
 435 440 445
 Glu Val Cys Ser Leu Leu Leu Ser His Gly Ala Asp Pro Thr Leu Val
 450 455 460
 Asn Cys His Gly Lys Ser Ala Val Asp Met Ala Pro Thr Pro Glu Leu
 465 470 475 480
 Arg Glu Arg Leu Thr Tyr Glu Phe Lys Gly His Ser Leu Leu Gln Ala
 485 490 495
 Ala Arg Glu Ala Asp Leu Ala Lys Val Lys Lys Thr Leu Ala Leu Glu
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 Ile Ile Asn Phe Lys Gln Pro Gln Ser His Glu Thr Ala Leu His Cys
 515 520 525
 Ala Val Ala Ser Leu His Pro Lys Arg Lys Gln Val Thr Glu Leu Leu
 530 535 540
 Leu Arg Lys Gly Ala Asn Val Asn Glu Lys Asn Lys Asp Phe Met Thr
 545 550 555 560
 Pro Leu His Val Ala Ala Glu Arg Ala His Asn Asp Val Met Glu Val
 565 570 575
 Leu His Lys His Gly Ala Lys Met Asn Ala Leu Asp Thr Leu Gly Gln
 580 585 590
 Thr Ala Leu His Arg Ala Ala Leu Ala Gly His Leu Gln Thr Cys Arg
 595 600 605
 Leu Leu Leu Ser Tyr Gly Ser Asp Pro Ser Ile Ile Ser Leu Gln Gly
 610 615 620
 Phe Thr Ala Ala Gln Met Gly Asn Glu Ala Val Gln Gln Ile Leu Ser
 625 630 635 640
 Glu Ser Thr Pro Ile Arg Thr Ser Asp Val Asp Tyr Arg Leu Leu Glu
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Ala Ser Lys Ala Gly Asp Leu Glu Thr Val Lys Gln Leu Cys Ser Ser
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 Gln Asn Val Asn Cys Arg Asp Leu Glu Gly Arg His Ser Thr Pro Leu
 675 680 685
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 690 695 700
 His His Gly Ala Asp Val His Ala Lys Asp Lys Gly Gly Leu Val Pro
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 Leu His Asn Ala Cys Ser Tyr Gly His Tyr Glu Val Ala Glu Leu Leu
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 Val Arg His Gly Ala Ser Val Asn Val Ala Asp Leu Trp Lys Phe Thr
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 Pro Leu His Glu Ala Ala Ala Lys Gly Lys Tyr Glu Ile Cys Lys Leu
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 Leu Leu Lys His Gly Ala Asp Pro Thr Lys Lys Asn Arg Asp Gly Asn
 770 775 780
 Thr Pro Leu Asp Leu Val Lys Glu Gly Asp Thr Asp Ile Gln Asp Leu
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 Leu Lys Gly Asp Ala Ala Leu Leu Asp Ala Ala Lys Lys Gly Cys Leu
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 Ala Arg Val Gln Lys Leu Cys Thr Pro Glu Asn Ile Asn Cys Arg Asp
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 Thr Gln Gly Arg Asn Ser Thr Pro Leu His Leu Ala Ala Gly Tyr Asn
 835 840 845
 Asn Leu Glu Val Ala Glu Tyr Leu Leu Glu His Gly Ala Asp Val Asn
 850 855 860
 Ala Gln Asp Lys Gly Gly Leu Ile Pro Leu His Asn Ala Ala Ser Tyr
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 Gly His Val Asp Ile Ala Ala Leu Leu Ile Lys Tyr Asn Thr Cys Val
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 Lys Gly Arg Thr Gln Leu Cys Ala Leu Leu Leu Ala His Gly Ala Asp
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 980 985 990
 Asp Asn Leu Thr Gly Pro Leu Ala Glu Leu Ala Val Gly Gly Ala Ser
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Leu Ala Asp Met Gly His Glu Glu Leu Lys Glu Ile Gly Ile Asn Ala
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Tyr Gly His Arg His Lys Leu Ile Lys Gly Val Glu Arg Leu Leu Gly
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Gly Gln Gln Gly Thr Asn Pro Tyr Leu Thr Phe His Cys Val Asn Gln
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Gly Thr Ile Leu Leu Asp Leu Ala Pro Glu Asp Lys Glu Tyr Gln Ser
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Val Val Asn Lys Lys Leu Arg Glu Arg Phe Cys His Arg Gln Lys Glu
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Val Ser Glu Glu Asn His Asn His His Asn Glu Arg Met Leu Phe His
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Gly Ser Pro Phe Ile Asn Ala Ile Ile His Lys Gly Phe Asp Glu Arg
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His Ala Tyr Ile Gly Gly Met Phe Gly Ala Gly Ile Tyr Phe Ala Glu
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Asn Ser Ser Lys Ser Asn Gln Tyr Val Tyr Gly Ile Gly Gly Gly Thr
 1220 1225 1230

Gly Cys Pro Thr His Lys Asp Arg Ser Cys Tyr Ile Cys His Arg Gln
 1235 1240 1245

Met Leu Phe Cys Arg Val Thr Leu Gly Lys Ser Phe Leu Gln Phe Ser
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Thr Met Lys Met Ala His Ala Pro Pro Gly His His Ser Val Ile Gly
 1265 1270 1275 1280

Arg Pro Ser Val Asn Gly Leu Ala Tyr Ala Glu Tyr Val Ile Tyr Arg
 1285 1290 1295

Gly Glu Gln Ala Tyr Pro Glu Tyr Leu Ile Thr Tyr Gln Ile Met Lys
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 35 40 45
 Gly Gly Thr Gly Cys Pro Val His Lys Asp Arg Ser Cys Tyr Ile Cys
 50 55 60
 His Arg Xaa Leu Leu Phe Cys Arg Val Thr Leu Gly Lys Ser Phe Leu
 65 70 75 80
 Gln Phe Ser Ala Met Lys Met Ala His Ser Pro Pro Gly His His Ser
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 Val Thr Gly Arg Pro Ser Val Asn Gly Leu Ala Leu Ala Glu Tyr Val
 100 105 110
 Ile Tyr Arg Gly Glu Gln
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 aacacagtat tgtattagta aaattagttc tgttgagggc attacagttt gttagaatca 180
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ccaaggggtgt taaacg

436

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<212> DNA

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tgctattttca tgggtctcct tttgtgaatg caattatcca caaaggcttt gatgaaaggc 60
atgctgtacat aggtggtatg tttggagctg gcattttattt tgctgaaaac tcttccaaaa 120
gcaatcaata tgtatatgga attggaggag gtactgggtg tccagttcac aaagacagat 180
cttgttacat ttgccacagg cagctgctct tttgccgggt aaccttgga aagtctttcc 240
tgcagttcag tgcaatgaaa atggcacatt ctctccagg tcatcactca gtcactggta 300
ggccccagtg aaatggccta gcattagctg naatatgtta tttacagagg agaacaggta 360
atgtagtttt aattttggtt catcttccaa aa 392
```

<210> 15

<211> 317

<212> DNA

<213> Homo sapiens

<400> 15

```
ttttttttgc agttctaaaa cagatttata ttacaaagca atgtaaataa atactgggct 60
agtacaaaag ctcttattta cagttttaca aatgaaattg tattcagtg aaatgctgtg 120
ttttaaagaa cacagtattg tattagtaaa attagttctg ttgagggcat tacagtttgt 180
taggaatcaa tgcataacat ataaaagggt caagttaact ctgtttataa tttaggtaca 240
gacaacccag ttttaaccggg gaatgggcat ctgttaaagt gctgaaaaaa cnggganata 300
tttaggaaaa cncgtga 317
```

<210> 16

<211> 485

<212> DNA

<213> Homo sapiens

<400> 16

```
tgcagttcta aaacagattt atattacaaa gcaatgtaaa taaatactgg gctagtacaa 60
aagctcttat ttacagtttt acaaatgaaa ttgtattcag tgtaaatgct gtgtttttaa 120
gaacacagta ttgtattagt aaaattagtt ctgttgaggg cattacagtt tgtagaatac 180
aatgcataac atataaaagg ttcaagttaa ctctgtttat aatttagtac agacaacca 240
gtttaacctg gaatggcatc tgttaaagtg ctgaaaaaac aggaatatatt tacgaaaaca 300
ctgtacatta ttaaagcttt atcaagtcag aatgttaaac ttctgttcaca tttttatcct 360
tttgccacag gcctgtgggg caagatgatt ttttttcagc aaaggagtaa aacgtagagg 420
gccactggct gctttgatga ttttaggggt cagtgggaat tagtttcta aaataacnat 480
ttatc 485
```

<210> 17

<211> 291

<212> DNA

<213> Homo sapiens

<400> 17

```
ttncctgcag ttcagtgcga tgaanatggc acattctcct ccaggtcatc actcagtcac 60
tggtagggcc agtgtaaatt gcctagcatt agctgaatat gttatttaca gaggagaaca 120
ggcttatcct gagtatttaa ttacttacca gattatgagg cctgaaggta tggctcgatgg 180
ataaatagtt attttaagaa actaatcca ctgaacctaa aatcatcaaa gcagcagtg 240
cctctacgtt ttactccttt gctgaaaaaa aatcatcttg cccacaggcc t 291
```

<210> 18

<211> 371

<212> DNA

<213> Homo sapiens

<400> 18

```
cgtagaggcc actgctgctt tgatganttt tanggttcan gtggaattng tttcttaaaa 60
taactattta tccatcgacc ataccttcag gcctcataat ctggtaagta attaaatact 120
```


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```

caggataaagc ctgttctcct ctgtaaataa catattcagc taatgctagg ccatttacac 180
tgggcctacc agtgactgaa gtgatgcctg gggggagaat gtgccatctt cattgcactg 240
aactgcaggn aagactttcc caagggttac ccgggcaaaa gagcagctgc ctgtgggnaa 300
tgttacaagg tcttgtcttt tgtngacctn gggcaccccg taccctcctc caattccata 360
tacatatttg a 371

```

<210> 19
 <211> 341
 <212> DNA
 <213> Homo sapiens

```

<400> 19
gaaagataca ctcaccggag aaaagaagtt tctgaagaaa accacaacca tgccaatgaa 60
cgaatgctat ttcatgggtc tccttttgtg aatgcaatta tccacaaagg ctttgatgaa 120
aggcatgcgt acataggctg tatgtttgga gctggcattt attttgctgg aaaactcttc 180
caaaaggcaa tcaatatgta tatgggaatt gggaggagg gtactgggg gtccagtttc 240
acaaaggaca gatcttgttt acatttggcc acaggcaggc tggctctttt tgcccgggtt 300
accttggggg aagtcttttc ctggcagttt cagttgccat g 341

```

<210> 20
 <211> 385
 <212> DNA
 <213> Homo sapiens

```

<400> 20
tactaaatta taaacagagt taacttgaac cttttatatg ttatgcattg attctaacaa 60
actgtaatgc cctcaacaga actaatttta ctaatacaat aangtgttct ttaaaacaca 120
gcatttacac tgaatacaat ttcatttga aaactgtaaa taagagcttt tgtactagcc 180
cagtatttat ttacattgct ttgtaatata aatctgtttt aggaactgca ggcggtttac 240
aaaatTTTTT catatgtatt gtccatttat acttcatctt acatcgtcat ggattgaggt 300
gatctttaca tttggattcc ngggggctat ggttcagggt gttagggttg gggaaagggt 360
tggggtttat ccgggnttta ntttg 385

```

<210> 21
 <211> 335
 <212> DNA
 <213> Homo sapiens

```

<400> 21
gaagggtatg tcgatggata aatagttatt ttaagaaact aattccactg aacctaaaat 60
catcaaagca gcagtgccct ctacgtttta ctcctttgct gaaaaaaaat catcttgccc 120
acaggcctgt ggcataaagg taaaaatgtg aacgaagttt aacattctga cttgataaag 180
ctttaataat gtacagtgtt ttctaaatat ttctgtttt ttcagcactt taacagatgc 240
cattccgggt taaactgggg ttgtctgtac taaattatta aacagngtta acttggaaac 300
nttttatatg ttatggcctt ggttcttaac caana 335

```

<210> 22
 <211> 388
 <212> DNA
 <213> Homo sapiens

```

<400> 22
gttttactcc tttgctgaaa aaaaatcatc ttgcccacag gcctgtggaa naaggataaa 60
aatgtgaacg aagttttaaca ttctgacttg ataaagcttt aataatgtac agtggtttct 120
aaatatttcc tgttttttca gcactttaac agatgccatt ccaggttaaa ctgggttgte 180
tgtactaaat tataaacaga gttaacttga accttttata tgttatgcat tgattctaac 240
aaactgtaat gccctcaaca gaactaattt tactaataca atactgtgtt ctttaaaaca 300
caggcattta cactggaata caatttcatt tggtaaaact ggtaantagg agcttttgta 360
ctagcccagt atttatttac atgctttg 388

```

<210> 23
 <211> 401
 <212> DNA
 <213> Homo sapiens

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<400> 23
 gttttactcc tttgctgaaa aaaaatcatc ttgcccacag gcctgtggaa naaggataaa 60
 aatgtgaacg aagttaacat tctgacttga taaagcttta ataatgtaca gtgttttcta 120
 aatatttcct gttttttcag cactttaaca gatgccatc cagggttaac tgggttgct 180
 gtactaaatt ataaacagag ttaacttgaa ccttttata gtatgcatt gattctaaca 240
 aactgtaatg cctcaacag aactantttt acttaataca atactgtgtt ctttnaaaac 300
 acaggcattt acactggaat acaattttca ttttggttaa actgggttaa ttaaggnggc 360
 tttttgtact nggccccgtn ttttatttta cattgctttg g 401

<210> 24
 <211> 354
 <212> DNA
 <213> Homo sapiens

<400> 24
 taattttact aatacaatac tgtgttcttt aaaacacagc atttacactg aatacaattt 60
 catttgtaaa actgtaaata agagcttttg tactagccca gtatttattt acattgcttt 120
 gtaataataa tctgttttag aactgcagcg gtttacaata ttttttcata tgtattgttc 180
 atctatactt catcttacat cgtcatgatt gagtgatctt tacatttgat tccagaggct 240
 atgttcagtt gttagttggg aaagattgag ttatcagatt taatttgccg atgggagcct 300
 ttatctgtca ttagaaatct ttctnattta agaacttatg aatatgctga agat 354

<210> 25
 <211> 18
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:Primer

<400> 25
 tgtaaaacga cggccagt 18

<210> 26
 <211> 19
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:Primer

<400> 26
 ggaaacagct atgaccatg 19

<210> 27
 <211> 18
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:Primer

<400> 27
 tttgccgggt aaccttgg 18

<210> 28
 <211> 18
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:Primer

<400> 28
 ccaagggttac ccggcaaa 18

- 23 -

<210> 29
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 29
gtaggccag tgtaaag 18

<210> 30
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 30
cattacact gggcctac 18

<210> 31
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 31
gagtaagtg cagggcatgt 20

<210> 32
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 32
acatgccctg caacttactc 20

<210> 33
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 33
gaatcaccgc agttactaaa 20

<210> 34
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 34

-24-

tttagtaact gcggtgattc 20

<210> 35
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 35
ggcctgaagg tatggtcgat 20

<210> 36
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 36
atcgaccata ccttcaggcc 20

<210> 37
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 37
tgagggcatt acagtttggt 20

<210> 38
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 38
taatacgaac tcactatagg g 21

<210> 39
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 39
atacactcac cggagaaa 18

<210> 40
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

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<400> 40
tttctccggt gagtgtat

18

<210> 41
<211> 1691
<212> DNA
<213> Artificial Sequence

<220>
<221> CDS
<222> (1)..(357)

<220>
<223> Description of Artificial Sequence: Sequence not
specified as protein-coding is vector sequence

<400> 41
atg cta ttt cat ggg tct cct ttt gtg aat gca att atc cac aaa ggc 48
Met Leu Phe His Gly Ser Pro Phe Val Asn Ala Ile Ile His Lys Gly
1 5 10 15
ttt gat gaa agg cat gcg tac ata ggt ggt atg ttt gga gct ggc att 96
Phe Asp Glu Arg His Ala Tyr Ile Gly Gly Met Phe Gly Ala Gly Ile
20 25 30
tat ttt gct gaa aac tct tcc aaa agc aat caa tat gta tat gga att 144
Tyr Phe Ala Glu Asn Ser Ser Lys Ser Asn Gln Tyr Val Tyr Gly Ile
35 40 45
gga gga ggt act ggg tgt cca gtt cac aaa gac aga tct tgt tac att 192
Gly Gly Gly Thr Gly Cys Pro Val His Lys Asp Arg Ser Cys Tyr Ile
50 55 60
tgc cac agg cag ctg ctc ttt tgc cgg gta acc ttg gga aag tct ttc 240
Cys His Arg Gln Leu Leu Phe Cys Arg Val Thr Leu Gly Lys Ser Phe
65 70 75 80
ctg cag ttc agt gca atg aaa atg gca cat tct cct cca ggt cat cac 288
Leu Gln Phe Ser Ala Met Lys Met Ala His Ser Pro Pro Gly His His
85 90 95
tca gtc act ggt agg ccc agt gta aat ggc cta gca tta gct gaa tat 336
Ser Val Thr Gly Arg Pro Ser Val Asn Gly Leu Ala Leu Ala Glu Tyr
100 105 110
gtt att tac aga gga gaa cag gtaagtgtt tttatttgtt catcttcaaa 387
Val Ile Tyr Arg Gly Glu Gln
115
aatgctaggg aggcatactt taacttttta ttaatctctt gaattgacaa gacatattgc 447
cttaactgga ttttttaaaa attttatttg gagataattt cagatttgga aagttacaaa 507
aatagtaaag agaattttct tataaccttt acctagattt cctaaatgtt aatattttgt 567
tctctttttt actcttacca ttctctcctt ctttccttgt gtgtgtacct atttttttgt 627
gaactgtttg agagtaagtt gcagggcag tccctttacc attaactatt tcaattgtaa 687
atttcttaaa aacaagaaga ttttattcaa atttcgccag tegtccgga tttttcttag 747
ctcttataaa taattgaaat cttgtattta acagcctgtc catagcaaag aagtatataa 807
ctgtgttttg ctctcagtga gagccaaaag tagttctaga gcagtgttgt gaactgggag 867
taggtatcgg aatcacccga gttactaaaa tcagacatga ttttagtctt atctgatact 927
tatgaactta gtattcatct tagacttgct gattgaaaat ctgaagaact gtactcaggg 987

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taaagatggt ttgagaaaat gtccttagat gattctgac tacaacagta atttagaacc 1047
 tcctccctaa gattaggaat acttccggaa agtctgttta tctttcaaga aaatttttgt 1107
 accattatgt gaatttatct ttctcttcca ggcttatcct gagtatttaa ttacttacca 1167
 gattatgagg cctgaaggta tggctgatgg ataaatagtt attttaagaa actaattcca 1227
 ctgaacctaa aatcatcaaa gcagcagtg cctctacgtt ttactccttt gctgaaaaaa 1287
 aatcatcttg cccacaggcc tggggcaaaa ggataaaaat gtgaacgaag ttttaacattc 1347
 tgacttgata agcttttaat aatgtacagt gttttctaaa tatttcctgt tttttcagca 1407
 ctttaacaga tgccattcca gggttaaactg ggttgctctg actaaattat aaacagagtt 1467
 aacttgaacc ttttatatgt tatgcattga ttctaacaaa ctgtaatgcc ctcaacagaa 1527
 ctaattttag taatacaata ctgtgttctt taaaacacag catttacact gaatacaatt 1587
 tcatttgtaa aactgtaaat aagagctttt gtactagccc agtattttatt tacattgctt 1647
 tgtaataata tcctgtttta gaagtgcata aaaaaaaaaa aaaa 1691

<210> 42

<211> 119

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence: Sequence not
specified as protein-coding is vector sequence

<400> 42

Met Leu Phe His Gly Ser Pro Phe Val Asn Ala Ile Ile His Lys Gly
1 5 10 15

Phe Asp Glu Arg His Ala Tyr Ile Gly Gly Met Phe Gly Ala Gly Ile
20 25 30

Tyr Phe Ala Glu Asn Ser Ser Lys Ser Asn Gln Tyr Val Tyr Gly Ile
35 40 45

Gly Gly Gly Thr Gly Cys Pro Val His Lys Asp Arg Ser Cys Tyr Ile
50 55 60

Cys His Arg Gln Leu Leu Phe Cys Arg Val Thr Leu Gly Lys Ser Phe
65 70 75 80

Leu Gln Phe Ser Ala Met Lys Met Ala His Ser Pro Pro Gly His His
85 90 95

Ser Val Thr Gly Arg Pro Ser Val Asn Gly Leu Ala Leu Ala Glu Tyr
100 105 110

Val Ile Tyr Arg Gly Glu Gln
115

<210> 43

<211> 1692

<212> DNA

<213> Artificial Sequence

<220>

<221> CDS

<222> (1) .. (357)

<220>

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<223> Description of Artificial Sequence: Sequence not specified as protein-coding is vector sequence

<400> 43

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atg cta ttt cat ggg tct cct ttt gtg aat gca att atc cac aaa ggc 48
Met Leu Phe His Gly Ser Pro Phe Val Asn Ala Ile Ile His Lys Gly
  1           5           10          15

ttt gat gaa agg cat gcg tac ata ggt ggt atg ttt gga gct ggc att 96
Phe Asp Glu Arg His Ala Tyr Ile Gly Gly Met Phe Gly Ala Gly Ile
          20          25          30

tat ttt gct gaa aac tct tcc aaa agc aat caa tat gta tat gga att 144
Tyr Phe Ala Glu Asn Ser Ser Lys Ser Asn Gln Tyr Val Tyr Gly Ile
          35          40          45

gga gga ggt act ggg tgt cca gtt cac aaa gac aga tct tgt tac att 192
Gly Gly Gly Thr Gly Cys Pro Val His Lys Asp Arg Ser Cys Tyr Ile
          50          55          60

tgc cac agg cag ctg ctc ttt tgc cgg gta acc ttg gga aag tct ttc 240
Cys His Arg Gln Leu Leu Phe Cys Arg Val Thr Leu Gly Lys Ser Phe
          65          70          75          80

ctg cag ttc agt gca atg aaa atg gca cat tct cct cca ggt cat cac 288
Leu Gln Phe Ser Ala Met Lys Met Ala His Ser Pro Pro Gly His His
          85          90          95

tca gtc act ggt agg ccc agt gta aat ggc cta gca tta gct gaa tat 336
Ser Val Thr Gly Arg Pro Ser Val Asn Gly Leu Ala Leu Ala Glu Tyr
          100          105          110

gtt att tac aga gga gaa cag gtaattgagt tttatttggt catcttcaaa 387
Val Ile Tyr Arg Gly Glu Gln
          115

aatgctaggg aggcatactt taacttttta ttaatctctt gaattgacaa gacataattgc 447

cttaactgga ttttttaaaa attttatttg gagataattt cagatttgga aagttacaaa 507

aatagtaaaag agaattttct tataaccttt acctagattt cctaaatggt aatattttgt 567

tctctttttt actcttacca ttctctctt ctttccttgt gtgtgtacct atttttttgt 627

gaactgtttg agagtaagtt gcagggcattg tccctttacc attaactatt tcaattgtaa 687

atttcctaaa aacaagaaga ttttattcaa atttcgccag tcgttcggga tttttcttag 747

ctcttataaa taattgaaat ctgtatttta acagcctgtc catagcaaag aagtatataa 807

ctgtgttttg ctctcagtga gagccaaaag tagttctaga gcagtgttgt gaactgggag 867

taggtatcgg aatcaccgca gttactaaaa tcagacatga ttttagtctt atctgatact 927

tatgaactta gtattcatct tagacttgct gattgaaaat ctgaagaact gtactcaggg 987

taaagatggt ttgagaaaat gtccctagat gattctgata tacaacagta atttagaacc 1047

tcctccctaa gattaggaat acttcgggaa agtctgttta tctttcaaga aaatttttgt 1107

accattattt gaatttatct ttctcttcca ggcttctcct gagtatttaa ttacttacca 1167

gattatgagg cctgaaggta tggtcgatgg ataaatagtt attttaagaa actaattcca 1227

ctgaacctaa aatcatcaaa gcagcagtgg cctctacgtt ttactccttt gctgaaaaaa 1287

aatcatcttg ccacagggc tgtggcaaaa ggataaaaat gtgaacgaag tttaacattc 1347

tgacttgata aagctttaat aatgtacagt gttttctaaa ttttctctgt tttttcagca 1407

```

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ctttaacaga tgccattcca gggttaaactg ggttgtctgt actaaattat aaacagagtt 1467
 aactgaacc ttttatatgt tatgcattga ttctaacaaa ctgtaatgcc ctcaacagaa 1527
 ctaattttac taatacaata ctgtgttctt taaaacacag catttacact gaatacaatt 1587
 tcatttgtaa aactgtaaat aagagctttt gtactagccc agtatttatt tacattgctt 1647
 tgtaataataa atctgtttta gaactgcaaa aaaaaaaaaa aaaaa 1692

<210> 44

<211> 119

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence: Sequence not specified as protein-coding is vector sequence

<400> 44

Met	Leu	Phe	His	Gly	Ser	Pro	Phe	Val	Asn	Ala	Ile	Ile	His	Lys	Gly
1				5					10					15	
Phe	Asp	Glu	Arg	His	Ala	Tyr	Ile	Gly	Gly	Met	Phe	Gly	Ala	Gly	Ile
			20					25					30		
Tyr	Phe	Ala	Glu	Asn	Ser	Ser	Lys	Ser	Asn	Gln	Tyr	Val	Tyr	Gly	Ile
		35					40					45			
Gly	Gly	Gly	Thr	Gly	Cys	Pro	Val	His	Lys	Asp	Arg	Ser	Cys	Tyr	Ile
	50				55					60					
Cys	His	Arg	Gln	Leu	Leu	Phe	Cys	Arg	Val	Thr	Leu	Gly	Lys	Ser	Phe
65				70					75					80	
Leu	Gln	Phe	Ser	Ala	Met	Lys	Met	Ala	His	Ser	Pro	Pro	Gly	His	His
				85					90					95	
Ser	Val	Thr	Gly	Arg	Pro	Ser	Val	Asn	Gly	Leu	Ala	Leu	Ala	Glu	Tyr
			100					105						110	
Val	Ile	Tyr	Arg	Gly	Glu	Gln									
						115									

<210> 45

<211> 582

<212> DNA

<213> Artificial Sequence

<220>

<221> CDS

<222> (1)..(480)

<220>

<223> Description of Artificial Sequence: Sequence not specified as protein-coding is vector sequence

<400> 45

gaa	aga	tac	act	cac	cgg	aga	aaa	gaa	gtt	tct	gaa	gaa	aac	cac	aac	48
Glu	Arg	Tyr	Thr	His	Arg	Arg	Lys	Glu	Val	Ser	Glu	Glu	Asn	His	Asn	
1				5					10					15		
cat	gcc	aat	gaa	cga	atg	cta	ttt	cat	ggg	tct	cct	ttt	gtg	aat	gca	96
His	Ala	Asn	Glu	Arg	Met	Leu	Phe	His	Gly	Ser	Pro	Phe	Val	Asn	Ala	
			20					25					30			
att	atc	cac	aaa	ggc	ttt	gat	gaa	agg	cat	gcg	tac	ata	ggg	ggg	atg	144
Ile	Ile	His	Lys	Gly	Phe	Asp	Glu	Arg	His	Ala	Tyr	Ile	Gly	Gly	Met	
			35				40					45				

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```

ttt gga gct ggc att tat ttt gct gaa aac tct tcc aaa agc aat caa 192
Phe Gly Ala Gly Ile Tyr Phe Ala Glu Asn Ser Ser Lys Ser Asn Gln
    50                55                60

tat gta tat gga att gga gga ggt act ggg tgt cca gtt cac aaa gac 240
Tyr Val Tyr Gly Ile Gly Gly Gly Thr Gly Cys Pro Val His Lys Asp
    65                70                75                80

aga tct tgt tac att tgc cac agg cag ctg ctc ttt tgc cgg gta acc 288
Arg Ser Cys Tyr Ile Cys His Arg Gln Leu Leu Phe Cys Arg Val Thr
    85                90                95

ttg gga aag tct ttc ctg cag ttc agt gca atg aaa atg gca cat tct 336
Leu Gly Lys Ser Phe Leu Gln Phe Ser Ala Met Lys Met Ala His Ser
    100                105                110

cct cca ggt cat cac tca gtc act ggt agg ccc agt gta aat ggc cta 384
Pro Pro Gly His His Ser Val Thr Gly Arg Pro Ser Val Asn Gly Leu
    115                120                125

gca tta gct gaa tat gtt att tac aga gga gaa cag gct tat cct gag 432
Ala Leu Ala Glu Tyr Val Ile Tyr Arg Gly Glu Gln Ala Tyr Pro Glu
    130                135                140

tat tta att act tac cag att atg agg cct gaa ggt atg gtc gat gga 480
Tyr Leu Ile Thr Tyr Gln Ile Met Arg Pro Glu Gly Met Val Asp Gly
    145                150                155                160

taa atag tta tttta gaaa cta attccac tgaacctaaa atcatcaaag cagcagtggc 540
ctctacgttt tactcctttg ctgaaaaaaa aaaaaaaaaa aa 582

```

<210> 46

<211> 160

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence: Sequence not specified as protein-coding is vector sequence

<400> 46

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Glu Arg Tyr Thr His Arg Arg Lys Glu Val Ser Glu Glu Asn His Asn
  1                5                10                15

His Ala Asn Glu Arg Met Leu Phe His Gly Ser Pro Phe Val Asn Ala
    20                25                30

Ile Ile His Lys Gly Phe Asp Glu Arg His Ala Tyr Ile Gly Gly Met
    35                40                45

Phe Gly Ala Gly Ile Tyr Phe Ala Glu Asn Ser Ser Lys Ser Asn Gln
    50                55                60

Tyr Val Tyr Gly Ile Gly Gly Gly Thr Gly Cys Pro Val His Lys Asp
    65                70                75                80

Arg Ser Cys Tyr Ile Cys His Arg Gln Leu Leu Phe Cys Arg Val Thr
    85                90                95

Leu Gly Lys Ser Phe Leu Gln Phe Ser Ala Met Lys Met Ala His Ser
    100                105                110

Pro Pro Gly His His Ser Val Thr Gly Arg Pro Ser Val Asn Gly Leu
    115                120                125

Ala Leu Ala Glu Tyr Val Ile Tyr Arg Gly Glu Gln Ala Tyr Pro Glu
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Tyr Leu Ile Thr Tyr Gln Ile Met Arg Pro Glu Gly Met Val Asp Gly
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acagttcgag agcacagaga tggaggtcat gcaggtggaa tcttcaacag atacaatatt 180
ctcaagattc agaaggtttg taacaagaaa ctatgggaaa gatacactca ccggagaaaa 240
gaagtttctg aagaaaacca caacctgccc aatgaacgaa tgctatttca tgggtctcct 300
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ccggacaaca aggtcttaac

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1 5 10 15	
gaa ttc ttg act cct ctg cac gtg gca tct gag aaa gct cat aat gat	96
Glu Phe Leu Thr Pro Leu His Val Ala Ser Glu Lys Ala His Asn Asp	
20 25 30	
gtt gtt gaa gta gtg gtg aaa cat gaa gca aag gtt aat gct ctg gat	144
Val Val Glu Val Val Val Lys His Glu Ala Lys Val Asn Ala Leu Asp	
35 40 45	
aat ctt ggt cag act tct cta cac aga gct gca tat tgt ggt cat cta	192
Asn Leu Gly Gln Thr Ser Leu His Arg Ala Ala Tyr Cys Gly His Leu	
50 55 60	
caa acc tgc cgc cta ctc ctg agc tat ggg tgt gat cct aac att ata	240
Gln Thr Cys Arg Leu Leu Ser Tyr Gly Cys Asp Pro Asn Ile Ile	
65 70 75 80	
tcc ctt cag ggc ttt act gct tta cag atg gga aat gaa aat gta cag	288
Ser Leu Gln Gly Phe Thr Ala Leu Gln Met Gly Asn Glu Asn Val Gln	
85 90 95	
caa ctc ctc caa gag ggt atc tca tta ggt aat tca gag gca gac aga	336
Gln Leu Leu Glu Gly Ile Ser Leu Gly Asn Ser Glu Ala Asp Arg	
100 105 110	
caa ttg ctg gaa gct gca aag gct gga gat gtc gaa act gta aaa aaa	384
Gln Leu Leu Glu Ala Ala Lys Ala Gly Asp Val Glu Thr Val Lys Lys	
115 120 125	
ctg tgt act gtt cag agt gtc aac tgc aga gac att gaa ggg cgt cag	432
Leu Cys Thr Val Gln Ser Val Asn Cys Arg Asp Ile Glu Gly Arg Gln	
130 135 140	
tct aca cca ctt cat ttt gca gct ggg tat aac aga gtg tcc gtg gtg	480
Ser Thr Pro Leu His Phe Ala Ala Gly Tyr Asn Arg Val Ser Val Val	
145 150 155 160	
gaa tat ctg cta cag cat gga gct gat gtg cat gct aaa gat aaa gga	528
Glu Tyr Leu Leu Gln His Gly Ala Asp Val His Ala Lys Asp Lys Gly	
165 170 175	
ggc ctt gta cct ttg cac aat gca tgt tct tat gga cat tat gaa gtt	576
Gly Leu Val Pro Leu His Asn Ala Cys Ser Tyr Gly His Tyr Glu Val	
180 185 190	
gca gaa ctt ctt gtt aaa cat gga gca gta gtt aat gta gct gat tta	624
Ala Glu Leu Leu Val Lys His Gly Ala Val Val Asn Val Ala Asp Leu	
195 200 205	
tgg aaa ttt aca cct tta cat gaa gca gca gca aaa gga aaa tat gaa	672
Trp Lys Phe Thr Pro Leu His Glu Ala Ala Ala Lys Gly Lys Tyr Glu	
210 215 220	

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att tgc aaa ctt ctg ctc cag cat ggt gca gac cct aca aaa aaa aac	720
Ile Cys Lys Leu Leu Leu Gln His Gly Ala Asp Pro Thr Lys Lys Asn	
225 230 235 240	
agg gat gga aat act cct ttg gat ctt gtt aaa gat gga gat aca gat	768
Arg Asp Gly Asn Thr Pro Leu Asp Leu Val Lys Asp Gly Asp Thr Asp	
245 250 255	
att caa gat ctg ctt agg gga gat gca gct ttg cta gat gct gcc aag	816
Ile Gln Asp Leu Leu Arg Gly Asp Ala Ala Leu Leu Asp Ala Ala Lys	
260 265 270	
aag ggt tgt tta gcc aga gtg aag aag ttg tct tct cct gat aat gta	864
Lys Gly Cys Leu Ala Arg Val Lys Lys Leu Ser Ser Pro Asp Asn Val	
275 280 285	
aat tgc cgc gat acc caa ggc aga cat tca aca cct tta cat tta gca	912
Asn Cys Arg Asp Thr Gln Gly Arg His Ser Thr Pro Leu His Leu Ala	
290 295 300	
gct ggt tat aat aat tta gaa gtt gca gag tat ttg tta caa cac gga	960
Ala Gly Tyr Asn Asn Leu Glu Val Ala Glu Tyr Leu Leu Gln His Gly	
305 310 315 320	
gct gat gtg aat gcc caa gac aaa gga gga ctt att cct tta cat aat	1008
Ala Asp Val Asn Ala Gln Asp Lys Gly Gly Leu Ile Pro Leu His Asn	
325 330 335	
gca gca tct tac ggg cat gta gat gta gca gct cta cta ata aag tat	1056
Ala Ala Ser Tyr Gly His Val Asp Val Ala Ala Leu Leu Ile Lys Tyr	
340 345 350	
aat gca tgt gtc aat gcc acg gac aaa tgg gct ttc aca cct ttg cac	1104
Asn Ala Cys Val Asn Ala Thr Asp Lys Trp Ala Phe Thr Pro Leu His	
355 360 365	
gaa gca gcc caa aag gga cga aca cag ctt tgt gct ttg ttg cta gcc	1152
Glu Ala Ala Gln Lys Gly Arg Thr Gln Leu Cys Ala Leu Leu Leu Ala	
370 375 380	
cat gga gct gac ccg act ctt aaa aat cag gaa gga caa aca cct tta	1200
His Gly Ala Asp Pro Thr Leu Lys Asn Gln Glu Gly Gln Thr Pro Leu	
385 390 395 400	
gat tta gtt tca gca gat gat gtc agc gct ctt ctg aca gca gcc atg	1248
Asp Leu Val Ser Ala Asp Asp Val Ser Ala Leu Leu Thr Ala Ala Met	
405 410 415	
ccc cca tct gct ctg ccc tct tgt tac aag cct caa gtg ctc aat ggt	1296
Pro Pro Ser Ala Leu Pro Ser Cys Tyr Lys Pro Gln Val Leu Asn Gly	
420 425 430	
gtg aga agc cca gga gcc act gca gat gct ctc tct tca ggt cca tct	1344
Val Arg Ser Pro Gly Ala Thr Ala Asp Ala Leu Ser Ser Gly Pro Ser	
435 440 445	
agc cca tca agc ctt tct gca gcc agc agt ctt gac aac tta tct ggg	1392
Ser Pro Ser Ser Leu Ser Ala Ala Ser Ser Leu Asp Asn Leu Ser Gly	
450 455 460	
agt ttt tca gaa ctg tct tca gta gtt agt tca agt gga aca gag ggt	1440
Ser Phe Ser Glu Leu Ser Ser Val Val Ser Ser Ser Gly Thr Glu Gly	
465 470 475 480	
gct tcc agt ttg gag aaa aag gag gtt cca gga gta gat ttt agc ata	1488
Ala Ser Ser Leu Glu Lys Lys Glu Val Pro Gly Val Asp Phe Ser Ile	
485 490 495	

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act caa ttc gta agg aat ctt gga ctt gag cac cta atg gat ata ttt	1536
Thr Gln Phe Val Arg Asn Leu Gly Leu Glu His Leu Met Asp Ile Phe	
500 505 510	
gag aga gaa cag atc act ttg gat gta tta gtt gag atg ggg cac aag	1584
Glu Arg Glu Gln Ile Thr Leu Asp Val Leu Val Glu Met Gly His Lys	
515 520 525	
gag ctg aag gag att gga atc aat gct tat gga cat agg cac aaa cta	1632
Glu Leu Lys Glu Ile Gly Ile Asn Ala Tyr Gly His Arg His Lys Leu	
530 535 540	
att aaa gga gtc gag aga ctt atc tcc gga caa caa ggt ctt aac cca	1680
Ile Lys Gly Val Glu Arg Leu Ile Ser Gly Gln Gln Gly Leu Asn Pro	
545 550 555 560	
tat tta act ttg aac acc tct ggt agt gga aca att ctt ata gat ctg	1728
Tyr Leu Thr Leu Asn Thr Ser Gly Ser Gly Thr Ile Leu Ile Asp Leu	
565 570 575	
tct cct gat gat aaa gag ttt cag tct gtg gag gaa gag atg caa agt	1776
Ser Pro Asp Asp Lys Glu Phe Gln Ser Val Glu Glu Glu Met Gln Ser	
580 585 590	
aca gtt cga gag cac aga gat gga ggt cat gca ggt gga atc ttc aac	1824
Thr Val Arg Glu His Arg Asp Gly Gly His Ala Gly Gly Ile Phe Asn	
595 600 605	
aga tac aat att ctc aag att cag aag gtt tgt aac aag aaa cta tgg	1872
Arg Tyr Asn Ile Leu Lys Ile Gln Lys Val Cys Asn Lys Lys Leu Trp	
610 615 620	
gaa aga tac act cac cgg aga aaa gaa gtt tct gaa gaa aac cac aac	1920
Glu Arg Tyr Thr His Arg Arg Lys Glu Val Ser Glu Glu Asn His Asn	
625 630 635 640	
cat gcc aat gaa cga atg cta ttt cat ggg tct cct ttt gtg aat gca	1968
His Ala Asn Glu Arg Met Leu Phe His Gly Ser Pro Phe Val Asn Ala	
645 650 655	
att atc cac aaa ggc ttt gat gaa agg cat gcg tac ata ggt ggt atg	2016
Ile Ile His Lys Gly Phe Asp Glu Arg His Ala Tyr Ile Gly Gly Met	
660 665 670	
ttt gga gct ggc att tat ttt gct gaa aac tct tcc aaa agc aat caa	2064
Phe Gly Ala Gly Ile Tyr Phe Ala Glu Asn Ser Ser Lys Ser Asn Gln	
675 680 685	
tat gta tat gga att gga gga ggt act ggg tgt cca gtt cac aaa gac	2112
Tyr Val Tyr Gly Ile Gly Gly Gly Thr Gly Cys Pro Val His Lys Asp	
690 695 700	
aga tct tgt tac att tgc cac agg cag ctg ctc ttt tgc cgg gta acc	2160
Arg Ser Cys Tyr Ile Cys His Arg Gln Leu Leu Phe Cys Arg Val Thr	
705 710 715 720	
ttg gga aag tct ttc ctg cag ttc agt gca atg aaa atg gca cat tct	2208
Leu Gly Lys Ser Phe Leu Gln Phe Ser Ala Met Lys Met Ala His Ser	
725 730 735	
cct cca ggt cat cac tca gtc act ggt agg ccc agt gta aat ggc cta	2256
Pro Pro Gly His His Ser Val Thr Gly Arg Pro Ser Val Asn Gly Leu	
740 745 750	
gca tta gct gaa tat gtt att tac aga gga gaa cag gct tat cct gag	2304
Ala Leu Ala Glu Tyr Val Ile Tyr Arg Gly Glu Gln Ala Tyr Pro Glu	
755 760 765	

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tat tta att act tac cag att atg agg cct gaa ggt atg gtc gat gga 2352
 Tyr Leu Ile Thr Tyr Gln Ile Met Arg Pro Glu Gly Met Val Asp Gly
 770 775 780

taaatagtta ttttaagaaa ctaattccac tgaacctaaa atcatcaaag cagcagtggc 2412
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 aacataagta ggatgttaca tttccagggt gggaagggtg atcctaaatc atttcccaat 3312
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 20 25 30
 Val Val Glu Val Val Val Lys His Glu Ala Lys Val Asn Ala Leu Asp
 35 40 45
 Asn Leu Gly Gln Thr Ser Leu His Arg Ala Ala Tyr Cys Gly His Leu
 50 55 60
 Gln Thr Cys Arg Leu Leu Leu Ser Tyr Gly Cys Asp Pro Asn Ile Ile
 65 70 75 80
 Ser Leu Gln Gly Phe Thr Ala Leu Gln Met Gly Asn Glu Asn Val Gln
 85 90 95
 Gln Leu Leu Gln Glu Gly Ile Ser Leu Gly Asn Ser Glu Ala Asp Arg
 100 105 110
 Gln Leu Leu Glu Ala Ala Lys Ala Gly Asp Val Glu Thr Val Lys Lys
 115 120 125

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Leu Cys Thr Val Gln Ser Val Asn Cys Arg Asp Ile Glu Gly Arg Gln
 130 135 140
 Ser Thr Pro Leu His Phe Ala Ala Gly Tyr Asn Arg Val Ser Val Val
 145 150 155 160
 Glu Tyr Leu Leu Gln His Gly Ala Asp Val His Ala Lys Asp Lys Gly
 165 170 175
 Gly Leu Val Pro Leu His Asn Ala Cys Ser Tyr Gly His Tyr Glu Val
 180 185 190
 Ala Glu Leu Leu Val Lys His Gly Ala Val Val Asn Val Ala Asp Leu
 195 200 205
 Trp Lys Phe Thr Pro Leu His Glu Ala Ala Ala Lys Gly Lys Tyr Glu
 210 215 220
 Ile Cys Lys Leu Leu Leu Gln His Gly Ala Asp Pro Thr Lys Lys Asn
 225 230 235 240
 Arg Asp Gly Asn Thr Pro Leu Asp Leu Val Lys Asp Gly Asp Thr Asp
 245 250 255
 Ile Gln Asp Leu Leu Arg Gly Asp Ala Ala Leu Leu Asp Ala Ala Lys
 260 265 270
 Lys Gly Cys Leu Ala Arg Val Lys Lys Leu Ser Ser Pro Asp Asn Val
 275 280 285
 Asn Cys Arg Asp Thr Gln Gly Arg His Ser Thr Pro Leu His Leu Ala
 290 295 300
 Ala Gly Tyr Asn Asn Leu Glu Val Ala Glu Tyr Leu Leu Gln His Gly
 305 310 315 320
 Ala Asp Val Asn Ala Gln Asp Lys Gly Gly Leu Ile Pro Leu His Asn
 325 330 335
 Ala Ala Ser Tyr Gly His Val Asp Val Ala Ala Leu Leu Ile Lys Tyr
 340 345 350
 Asn Ala Cys Val Asn Ala Thr Asp Lys Trp Ala Phe Thr Pro Leu His
 355 360 365
 Glu Ala Ala Gln Lys Gly Arg Thr Gln Leu Cys Ala Leu Leu Leu Ala
 370 375 380
 His Gly Ala Asp Pro Thr Leu Lys Asn Gln Glu Gly Gln Thr Pro Leu
 385 390 395 400
 Asp Leu Val Ser Ala Asp Asp Val Ser Ala Leu Leu Thr Ala Ala Met
 405 410 415
 Pro Pro Ser Ala Leu Pro Ser Cys Tyr Lys Pro Gln Val Leu Asn Gly
 420 425 430
 Val Arg Ser Pro Gly Ala Thr Ala Asp Ala Leu Ser Ser Gly Pro Ser
 435 440 445
 Ser Pro Ser Ser Leu Ser Ala Ala Ser Ser Leu Asp Asn Leu Ser Gly
 450 455 460
 Ser Phe Ser Glu Leu Ser Ser Val Val Ser Ser Ser Gly Thr Glu Gly
 465 470 475 480
 Ala Ser Ser Leu Glu Lys Lys Glu Val Pro Gly Val Asp Phe Ser Ile
 485 490 495

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Thr Gln Phe Val Arg Asn Leu Gly Leu Glu His Leu Met Asp Ile Phe
 500 505 510
 Glu Arg Glu Gln Ile Thr Leu Asp Val Leu Val Glu Met Gly His Lys
 515 520 525
 Glu Leu Lys Glu Ile Gly Ile Asn Ala Tyr Gly His Arg His Lys Leu
 530 535 540
 Ile Lys Gly Val Glu Arg Leu Ile Ser Gly Gln Gln Gly Leu Asn Pro
 545 550 555 560
 Tyr Leu Thr Leu Asn Thr Ser Gly Ser Gly Thr Ile Leu Ile Asp Leu
 565 570 575
 Ser Pro Asp Asp Lys Glu Phe Gln Ser Val Glu Glu Glu Met Gln Ser
 580 585 590
 Thr Val Arg Glu His Arg Asp Gly Gly His Ala Gly Gly Ile Phe Asn
 595 600 605
 Arg Tyr Asn Ile Leu Lys Ile Gln Lys Val Cys Asn Lys Lys Leu Trp
 610 615 620
 Glu Arg Tyr Thr His Arg Arg Lys Glu Val Ser Glu Glu Asn His Asn
 625 630 635 640
 His Ala Asn Glu Arg Met Leu Phe His Gly Ser Pro Phe Val Asn Ala
 645 650 655
 Ile Ile His Lys Gly Phe Asp Glu Arg His Ala Tyr Ile Gly Gly Met
 660 665 670
 Phe Gly Ala Gly Ile Tyr Phe Ala Glu Asn Ser Ser Lys Ser Asn Gln
 675 680 685
 Tyr Val Tyr Gly Ile Gly Gly Gly Thr Gly Cys Pro Val His Lys Asp
 690 695 700
 Arg Ser Cys Tyr Ile Cys His Arg Gln Leu Leu Phe Cys Arg Val Thr
 705 710 715 720
 Leu Gly Lys Ser Phe Leu Gln Phe Ser Ala Met Lys Met Ala His Ser
 725 730 735
 Pro Pro Gly His His Ser Val Thr Gly Arg Pro Ser Val Asn Gly Leu
 740 745 750
 Ala Leu Ala Glu Tyr Val Ile Tyr Arg Gly Glu Gln Ala Tyr Pro Glu
 755 760 765
 Tyr Leu Ile Thr Tyr Gln Ile Met Arg Pro Glu Gly Met Val Asp Gly
 770 775 780

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 <213> Homo sapiens

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 Ala His Asn Asp Val Val Glu Val Val Lys His Glu Ala Lys
 1 5 10 15

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Val Asn Ala Leu Asp Asn Leu Gly Gln Thr Ser Leu His Arg Ala Ala	
20 25 30	
tat tgt ggt cat cta caa acc tgc cgc cta ctc ctg agc tat ggg tgt	143
Tyr Cys Gly His Leu Gln Thr Cys Arg Leu Leu Leu Ser Tyr Gly Cys	
35 40 45	
gat cct aac att ata tcc ctt cag ggc ttt act gct tta cag atg gga	191
Asp Pro Asn Ile Ile Ser Leu Gln Gly Phe Thr Ala Leu Gln Met Gly	
50 55 60	
aat gaa aat gta cag caa ctc ctc caa gag ggt atc tca tta ggt aat	239
Asn Glu Asn Val Gln Gln Leu Gln Glu Gly Ile Ser Leu Gly Asn	
65 70 75	
tca gag gca gac aga caa ttg ctg gaa gct gca aag gct gga gat gtc	287
Ser Glu Ala Asp Arg Gln Leu Leu Glu Ala Ala Lys Ala Gly Asp Val	
80 85 90 95	
gaa act gta aaa aaa ctg tgt act gtt cag agt gtc aac tgc aga gac	335
Glu Thr Val Lys Lys Leu Cys Thr Val Gln Ser Val Asn Cys Arg Asp	
100 105 110	
att gaa ggg cgt cag tct aca cca ctt cat ttt gca gct ggg tat aac	383
Ile Glu Gly Arg Gln Ser Thr Pro Leu His Phe Ala Ala Gly Tyr Asn	
115 120 125	
aga gtg tcc gtg gtg gaa tat ctg cta cag cat gga gct gat gtg cat	431
Arg Val Ser Val Val Glu Tyr Leu Leu Gln His Gly Ala Asp Val His	
130 135 140	
gct aaa gat aaa gga ggc ctt gta cct ttg cac aat gca tgt tct tat	479
Ala Lys Asp Lys Gly Gly Leu Val Pro Leu His Asn Ala Cys Ser Tyr	
145 150 155	
gga cat tat gaa gtt gca gaa ctt ctt gtt aaa cat gga gca gta gtt	527
Gly His Tyr Glu Val Ala Glu Leu Leu Val Lys His Gly Ala Val Val	
160 165 170 175	
aat gta gct gat tta tgg aaa ttt aca cct tta cat gaa gca gca gca	575
Asn Val Ala Asp Leu Trp Lys Phe Thr Pro Leu His Glu Ala Ala Ala	
180 185 190	
aaa gga aaa tat gaa att tgc aaa ctt ctg ctc cag cat ggt gca gac	623
Lys Gly Lys Tyr Glu Ile Cys Lys Leu Leu Gln His Gly Ala Asp	
195 200 205	
cct aca aaa aaa aac agg gat gga aat act cct ttg gat ctt gtt aaa	671
Pro Thr Lys Lys Asn Arg Asp Gly Asn Thr Pro Leu Asp Leu Val Lys	
210 215 220	
gat gga gat aca gat att caa gat ctg ctt agg gga gat gca gct ttg	719
Asp Gly Asp Thr Asp Ile Gln Asp Leu Leu Arg Gly Asp Ala Ala Leu	
225 230 235	
cta gat gct gcc aag aag ggt tgt tta gcc aga gtg aag aag ttg tct	767
Leu Asp Ala Ala Lys Lys Gly Cys Leu Ala Arg Val Lys Lys Leu Ser	
240 245 250 255	
tct cct gat aat gta aat tgc cgc gat acc caa ggc aga cat tca aca	815
Ser Pro Asp Asn Val Asn Cys Arg Asp Thr Gln Gly Arg His Ser Thr	
260 265 270	
cct tta cat tta gca gct ggt tat aat aat tta gaa gtt gca gag tat	863
Pro Leu His Leu Ala Ala Gly Tyr Asn Asn Leu Glu Val Ala Glu Tyr	
275 280 285	

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Leu Leu Gln His Gly Ala Asp Val Asn Ala Gln Asp Lys Gly Gly Leu	
290 295 300	
att cct tta cat aat gca gca tct tac ggg cat gta gat gta gca gct	959
Ile Pro Leu His Asn Ala Ala Ser Tyr Gly His Val Asp Val Ala Ala	
305 310 315	
cta cta ata aag tat aat gca tgt gtc aat gcc acg gac aaa tgg gct	1007
Leu Leu Ile Lys Tyr Asn Ala Cys Val Asn Ala Thr Asp Lys Trp Ala	
320 325 330 335	
ttc aca cct ttg cac gaa gca gcc caa aag gga cga aca cag ctt tgt	1055
Phe Thr Pro Leu His Glu Ala Ala Gln Lys Gly Arg Thr Gln Leu Cys	
340 345 350	
gct ttg ttg cta gcc cat gga gct gac ccg act ctt aaa aat cag gaa	1103
Ala Leu Leu Leu Ala His Gly Ala Asp Pro Thr Leu Lys Asn Gln Glu	
355 360 365	
gga caa aca cct tta gat tta gtt tca gca gat gat gtc agc gct ctt	1151
Gly Gln Thr Pro Leu Asp Leu Val Ser Ala Asp Asp Val Ser Ala Leu	
370 375 380	
ctg aca gca gcc atg ccc cca tct gct ctg ccc tct tgt tac aag cct	1199
Leu Thr Ala Ala Met Pro Pro Ser Ala Leu Pro Ser Cys Tyr Lys Pro	
385 390 395	
caa gtg ctc aat ggt gtg aga agc cca gga gcc act gca gat gct ctc	1247
Gln Val Leu Asn Gly Val Arg Ser Pro Gly Ala Thr Ala Asp Ala Leu	
400 405 410 415	
tct tca ggt cca tct agc cca tca agc ctt tct gca gcc agc agt ctt	1295
Ser Ser Gly Pro Ser Ser Pro Ser Ser Leu Ser Ala Ala Ser Ser Leu	
420 425 430	
gac aac tta tct ggg agt ttt tca gaa ctg tct tca gta gtt agt tca	1343
Asp Asn Leu Ser Gly Ser Phe Ser Glu Leu Ser Ser Val Val Ser Ser	
435 440 445	
agt gga aca gag ggt gct tcc agt ttg gag aaa aag gag gtt cca gga	1391
Ser Gly Thr Glu Gly Ala Ser Ser Leu Glu Lys Lys Glu Val Pro Gly	
450 455 460	
gta gat ttt agc ata act caa ttc gta agg aat ctt gga ctt gag cac	1439
Val Asp Phe Ser Ile Thr Gln Phe Val Arg Asn Leu Gly Leu Glu His	
465 470 475	
cta atg gat ata ttt gag aga gaa cag atc act ttg gat gta tta gtt	1487
Leu Met Asp Ile Phe Glu Arg Glu Gln Ile Thr Leu Asp Val Leu Val	
480 485 490 495	
gag atg ggg cac aag gag ctg aag gag att gga atc aat gct tat gga	1535
Glu Met Gly His Lys Glu Leu Lys Glu Ile Gly Ile Asn Ala Tyr Gly	
500 505 510	
cat agg cac aaa cta att aaa gga gtc gag aga ctt atc tcc gga caa	1583
His Arg His Lys Leu Ile Lys Gly Val Glu Arg Leu Ile Ser Gly Gln	
515 520 525	
caa ggt ctt aac cca tat tta act ttg aac acc tct ggt agt gga aca	1631
Gln Gly Leu Asn Pro Tyr Leu Thr Leu Asn Thr Ser Gly Ser Gly Thr	
530 535 540	
att ctt ata gat ctg tct cct gat gat aaa gag ttt cag tct gtg gag	1679
Ile Leu Ile Asp Leu Ser Pro Asp Asp Lys Glu Phe Gln Ser Val Glu	
545 550 555	

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gaa gag atg caa agt aca gtt cga gag cac aga gat gga ggt cat gca 1727
 Glu Glu Met Gln Ser Thr Val Arg Glu His Arg Asp Gly Gly His Ala
 560 565 570 575

ggt gga atc ttc aac aga tac aat att ctc aag att cag aag gtt tgt 1775
 Gly Gly Ile Phe Asn Arg Tyr Asn Ile Leu Lys Ile Gln Lys Val Cys
 580 585 590

aac aag aaa cta tgg gaa aga tac act cac cgg aga aaa gaa gtt tct 1823
 Asn Lys Lys Leu Trp Glu Arg Tyr Thr His Arg Arg Lys Glu Val Ser
 595 600 605

gaa gaa aac cac aac cat gcc aat gaa cga atg cta ttt cat ggg tct 1871
 Glu Glu Asn His Asn His Ala Asn Glu Arg Met Leu Phe His Gly Ser
 610 615 620

cct ttt gtg aat gca att atc cac aaa ggc ttt gat gaa agg cat gcg 1919
 Pro Phe Val Asn Ala Ile Ile His Lys Gly Phe Asp Glu Arg His Ala
 625 630 635

tac ata ggt ggt atg ttt gga gct ggc att tat ttt gct gaa aac tct 1967
 Tyr Ile Gly Gly Met Phe Gly Ala Gly Ile Tyr Phe Ala Glu Asn Ser
 640 645 650 655

tcc aaa agc aat caa tat gta tat gga att gga gga ggt act ggg tgt 2015
 Ser Lys Ser Asn Gln Tyr Val Tyr Gly Ile Gly Gly Gly Thr Gly Cys
 660 665 670

cca gtt cac aaa gac aga tct tgt tac att tgc cac agg cag ctg ctc 2063
 Pro Val His Lys Asp Arg Ser Cys Tyr Ile Cys His Arg Gln Leu Leu
 675 680 685

ttt tgc cgg gta acc ttg gga aag tct ttc ctg cag ttc agt gca atg 2111
 Phe Cys Arg Val Thr Leu Gly Lys Ser Phe Leu Gln Phe Ser Ala Met
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aaa atg gca cat tct cct cca ggt cat cac tca gtc act ggt agg ccc 2159
 Lys Met Ala His Ser Pro Pro Gly His His Ser Val Thr Gly Arg Pro
 705 710 715

agt gta aat ggc cta gca tta gct gaa tat gtt att tac aga gga gaa 2207
 Ser Val Asn Gly Leu Ala Leu Ala Glu Tyr Val Ile Tyr Arg Gly Glu
 720 725 730 735

cag gct tat cct gag tat tta att act tac cag att atg agg cct gaa 2255
 Gln Ala Tyr Pro Glu Tyr Leu Ile Thr Tyr Gln Ile Met Arg Pro Glu
 740 745 750

ggt atg gtc gat gga taaatagtta ttttaagaaa ctaattccac tgaacctaaa 2310
 Gly Met Val Asp Gly
 755

atcatcaaag cagcagtggc ctctacgttt tactcctttg ctgaaaaaaaa atcatcttgc 2370

ccacaggcct gtggcaaaag gataaaaatg tgaacgaagt ttaacattct gacttgataa 2430

agctttaata atgtacagtg ttttctaaat atttcctggt ttttcagcac tttaacagat 2490

gccattccag gttaaactgg gttgtctgta ctaaattata aacagagtta acttgaacct 2550

tttatatggt atgcattgat tctaacaaac tgtaatgccc tcaacagaac taattttact 2610

aatacaatac tgtgttcttt aaaacacagc atttacactg aatacaattt catttgtaaa 2670

actgtaaata agagcttttg tactagccca gtatttattt acattgcttt gtaatataaa 2730

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catctttacat cgtcatgatt gagtgatctt tacatttgat tccagaggct atgttcagtt 2850

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gttagtggg aaagattgag ttatcagatt taatttgcca ttaaaccctta tgggggttttc 2910
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 gttttgtaca tgtacataat atatttactt cctgctttca cattagtaat ctgagatggt 3750
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<211> 756

<212> PRT

<213> Homo sapiens

<400> 91

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Cys Gly His Leu Gln Thr Cys Arg Leu Leu Leu Ser Tyr Gly Cys Asp
 35 40 45

Pro Asn Ile Ile Ser Leu Gln Gly Phe Thr Ala Leu Gln Met Gly Asn
 50 55 60

Glu Asn Val Gln Gln Leu Leu Glu Gly Ile Ser Leu Gly Asn Ser
 65 70 75 80

Glu Ala Asp Arg Gln Leu Leu Glu Ala Ala Lys Ala Gly Asp Val Glu
 85 90 95

Thr Val Lys Lys Leu Cys Thr Val Gln Ser Val Asn Cys Arg Asp Ile
 100 105 110

Glu Gly Arg Gln Ser Thr Pro Leu His Phe Ala Ala Gly Tyr Asn Arg
 115 120 125

Val Ser Val Val Glu Tyr Leu Leu Gln His Gly Ala Asp Val His Ala
 130 135 140

Lys Asp Lys Gly Gly Leu Val Pro Leu His Asn Ala Cys Ser Tyr Gly
 145 150 155 160

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His Tyr Glu Val Ala Glu Leu Leu Val Lys His Gly Ala Val Val Asn
 165 170 175
 Val Ala Asp Leu Trp Lys Phe Thr Pro Leu His Glu Ala Ala Ala Lys
 180 185 190
 Gly Lys Tyr Glu Ile Cys Lys Leu Leu Leu Gln His Gly Ala Asp Pro
 195 200 205
 Thr Lys Lys Asn Arg Asp Gly Asn Thr Pro Leu Asp Leu Val Lys Asp
 210 215 220
 Gly Asp Thr Asp Ile Gln Asp Leu Leu Arg Gly Asp Ala Ala Leu Leu
 225 230 235 240
 Asp Ala Ala Lys Lys Gly Cys Leu Ala Arg Val Lys Lys Leu Ser Ser
 245 250 255
 Pro Asp Asn Val Asn Cys Arg Asp Thr Gln Gly Arg His Ser Thr Pro
 260 265 270
 Leu His Leu Ala Ala Gly Tyr Asn Asn Leu Glu Val Ala Glu Tyr Leu
 275 280 285
 Leu Gln His Gly Ala Asp Val Asn Ala Gln Asp Lys Gly Gly Leu Ile
 290 295 300
 Pro Leu His Asn Ala Ala Ser Tyr Gly His Val Asp Val Ala Ala Leu
 305 310 315 320
 Leu Ile Lys Tyr Asn Ala Cys Val Asn Ala Thr Asp Lys Trp Ala Phe
 325 330 335
 Thr Pro Leu His Glu Ala Ala Gln Lys Gly Arg Thr Gln Leu Cys Ala
 340 345 350
 Leu Leu Leu Ala His Gly Ala Asp Pro Thr Leu Lys Asn Gln Glu Gly
 355 360 365
 Gln Thr Pro Leu Asp Leu Val Ser Ala Asp Asp Val Ser Ala Leu Leu
 370 375 380
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 385 390 395 400
 Val Leu Asn Gly Val Arg Ser Pro Gly Ala Thr Ala Asp Ala Leu Ser
 405 410 415
 Ser Gly Pro Ser Ser Pro Ser Ser Leu Ser Ala Ala Ser Ser Leu Asp
 420 425 430
 Asn Leu Ser Gly Ser Phe Ser Glu Leu Ser Ser Val Val Ser Ser Ser
 435 440 445
 Gly Thr Glu Gly Ala Ser Ser Leu Glu Lys Lys Glu Val Pro Gly Val
 450 455 460
 Asp Phe Ser Ile Thr Gln Phe Val Arg Asn Leu Gly Leu Glu His Leu
 465 470 475 480
 Met Asp Ile Phe Glu Arg Glu Gln Ile Thr Leu Asp Val Leu Val Glu
 485 490 495
 Met Gly His Lys Glu Leu Lys Glu Ile Gly Ile Asn Ala Tyr Gly His
 500 505 510
 Arg His Lys Leu Ile Lys Gly Val Glu Arg Leu Ile Ser Gly Gln Gln
 515 520 525

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Gly Leu Asn Pro Tyr Leu Thr Leu Asn Thr Ser Gly Ser Gly Thr Ile
 530 535 540
 Leu Ile Asp Leu Ser Pro Asp Asp Lys Glu Phe Gln Ser Val Glu Glu
 545 550 555 560
 Glu Met Gln Ser Thr Val Arg Glu His Arg Asp Gly Gly His Ala Gly
 565 570 575
 Gly Ile Phe Asn Arg Tyr Asn Ile Leu Lys Ile Gln Lys Val Cys Asn
 580 585 590
 Lys Lys Leu Trp Glu Arg Tyr Thr His Arg Arg Lys Glu Val Ser Glu
 595 600 605
 Glu Asn His Asn His Ala Asn Glu Arg Met Leu Phe His Gly Ser Pro
 610 615 620
 Phe Val Asn Ala Ile Ile His Lys Gly Phe Asp Glu Arg His Ala Tyr
 625 630 635 640
 Ile Gly Gly Met Phe Gly Ala Gly Ile Tyr Phe Ala Glu Asn Ser Ser
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 Lys Ser Asn Gln Tyr Val Tyr Gly Ile Gly Gly Gly Thr Gly Cys Pro
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 Val His Lys Asp Arg Ser Cys Tyr Ile Cys His Arg Gln Leu Leu Phe
 675 680 685
 Cys Arg Val Thr Leu Gly Lys Ser Phe Leu Gln Phe Ser Ala Met Lys
 690 695 700
 Met Ala His Ser Pro Pro Gly His His Ser Val Thr Gly Arg Pro Ser
 705 710 715 720
 Val Asn Gly Leu Ala Leu Ala Glu Tyr Val Ile Tyr Arg Gly Glu Gln
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 Met Val Asp Gly
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<211> 2971

<212> DNA

<213> Homo sapiens

<400> 92

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 <213> Artificial Sequence

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 <223> Description of Artificial Sequence:Primer

<400> 93
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<210> 94
 <211> 20
 <212> DNA
 <213> Artificial Sequence

<220>
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<400> 94
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<210> 95
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<220>
 <223> Description of Artificial Sequence:Primer

<400> 95
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<210> 96
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<220>
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<210> 97
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<220>
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 Ala Ser Ala Ala Ala Glu Ala Val Glu Pro Ala Ala Arg Glu Leu Phe
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 Glu Ala Cys Arg Asn Gly Asp Val Glu Arg Val Lys Arg Leu Val Thr
 35 40 45
 cct gag aag gtg aac agc cgc gac acg gcg ggc agg aaa tcc acc ccg 193
 Pro Glu Lys Val Asn Ser Arg Asp Thr Ala Gly Arg Lys Ser Thr Pro
 50 55 60
 ctg cac ttc gcc gca ggt ttt ggg cgg aaa gac gta gtt gaa tat ttg 241
 Leu His Phe Ala Ala Gly Phe Gly Arg Lys Asp Val Val Glu Tyr Leu
 65 70 75 80
 ctt cag aat ggt gca aat gtc caa gca cgt gat gat ggg ggc ctt att 289
 Leu Gln Asn Gly Ala Asn Val Gln Ala Arg Asp Asp Gly Gly Leu Ile
 85 90 95
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 Pro Leu His Asn Ala Cys Ser Phe Gly His Ala Glu Val Val Asn Leu
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 Leu Leu Arg His Gly Ala Asp Pro Asn Ala Arg Asp Asn Trp Asn Tyr
 115 120 125
 act cct ctc cat gaa gct gca att aaa gga aag att gat gtt tgc att 433
 Thr Pro Leu His Glu Ala Ala Ile Lys Gly Lys Ile Asp Val Cys Ile
 130 135 140

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Val Leu Leu Gln His Gly Ala Glu Pro Thr Ile Arg Asn Thr Asp Gly	
145 150 155 160	
agg aca gca ttg gat tta gca gat cca tct gcc aaa gca gtg ctt act	529
Arg Thr Ala Leu Asp Leu Ala Asp Pro Ser Ala Lys Ala Val Leu Thr	
165 170 175	
ggt gaa tat aag aaa gat gaa ctc tta gaa agt gcc agg agt ggc aat	577
Gly Glu Tyr Lys Lys Asp Glu Leu Glu Ser Ala Arg Ser Gly Asn	
180 185 190	
gaa gaa aaa atg atg gct cta ctc aca cca tta aat gtc aac tgc cac	625
Glu Glu Lys Met Met Ala Leu Thr Pro Leu Asn Val Asn Cys His	
195 200 205	
gca agt gat ggc aga aag tca act cca tta cat ttg gca gca gga tat	673
Ala Ser Asp Gly Arg Lys Ser Thr Pro Leu His Leu Ala Ala Gly Tyr	
210 215 220	
aac aga gta aag att gta cag ctg tta ctg caa cat gga gct gat gtc	721
Asn Arg Val Lys Ile Val Gln Leu Leu Leu Gln His Gly Ala Asp Val	
225 230 235 240	
cat gct aaa gat aaa ggt gat ctg gta cca tta cac aat gcc tgt tct	769
His Ala Lys Asp Lys Gly Asp Leu Val Pro Leu His Asn Ala Cys Ser	
245 250 255	
tat ggt cat tat gaa gta act gaa ctt ttg gtc aag cat ggt gcc tgt	817
Tyr Gly His Tyr Glu Val Thr Glu Leu Leu Val Lys His Gly Ala Cys	
260 265 270	
gta aat gca atg gac ttg tgg caa ttc act cct ctt cat gag gca gct	865
Val Asn Ala Met Asp Leu Trp Gln Phe Thr Pro Leu His Glu Ala Ala	
275 280 285	
tct aag aac agg gtt gaa gta tgt tct ctt ctc tta agt tat ggt gca	913
Ser Lys Asn Arg Val Glu Val Cys Ser Leu Leu Leu Ser Tyr Gly Ala	
290 295 300	
gac cca aca ctg ctc aat tgt cac aat aaa agt gct ata gac ttg gct	961
Asp Pro Thr Leu Leu Asn Cys His Asn Lys Ser Ala Ile Asp Leu Ala	
305 310 315 320	
ccc aca cca cag tta aaa gaa aga tta gca tat gaa ttt aaa ggc cac	1009
Pro Thr Pro Gln Leu Lys Glu Arg Leu Ala Tyr Glu Phe Lys Gly His	
325 330 335	
tcg ttg ctg caa gct gca cga gaa gct gat gtt act cga atc aaa aaa	1057
Ser Leu Leu Gln Ala Ala Arg Glu Ala Asp Val Thr Arg Ile Lys Lys	
340 345 350	
cat ctc tct ctg gaa atg gtg aat ttc aag cat cct caa aca cat gaa	1105
His Leu Ser Leu Glu Met Val Asn Phe Lys His Pro Gln Thr His Glu	
355 360 365	
aca gca ttg cat tgt gct gct gca tct cca tat ccc aaa aga aag caa	1153
Thr Ala Leu His Cys Ala Ala Ala Ser Pro Tyr Pro Lys Arg Lys Gln	
370 375 380	
ata tgt gaa ctg ttg cta aga aaa gga gca aac atc aat gaa aag act	1201
Ile Cys Glu Leu Leu Leu Arg Lys Gly Ala Asn Ile Asn Glu Lys Thr	
385 390 395 400	
aaa gaa ttc ttg act cct ctg cac gtg gca tct gag aaa gct cat aat	1249
Lys Glu Phe Leu Thr Pro Leu His Val Ala Ser Glu Lys Ala His Asn	
405 410 415	

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gat gtt gtt gaa gta gtg gtg aaa cat gaa gca aag gtt aat gct ctg 1297
Asp Val Val Glu Val Val Val Lys His Glu Ala Lys Val Asn Ala Leu
420 425 430

gat aat ctt ggt cag act tct cta cac aga gct gca tat tgt ggt cat 1345
Asp Asn Leu Gly Gln Thr Ser Leu His Arg Ala Ala Tyr Cys Gly His
435 440 445

cta caa acc tgc cgc cta ctc ctg agc tat ggg tgt gat cct aac att 1393
Leu Gln Thr Cys Arg Leu Leu Ser Tyr Gly Cys Asp Pro Asn Ile
450 455 460

ata tcc ctt cag ggc ttt act gct tta cag atg gga aat gaa aat gta 1441
Ile Ser Leu Gln Gly Phe Thr Ala Leu Gln Met Gly Asn Glu Asn Val
465 470 475 480

cag caa ctc ctc caa gag ggt atc tca tta ggt aat tca gag gca gac 1489
Gln Gln Leu Leu Gln Gly Ile Ser Leu Gly Asn Ser Glu Ala Asp
485 490 495

aga caa ttg ctg gaa gct gca aag gct gga gat gtc gaa act gta aaa 1537
Arg Gln Leu Leu Glu Ala Ala Lys Ala Gly Asp Val Glu Thr Val Lys
500 505 510

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Lys Leu Cys Thr Val Gln Ser Val Asn Cys
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<213> Homo sapiens

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Glu Ala Cys Arg Asn Gly Asp Val Glu Arg Val Lys Arg Leu Val Thr
35 40 45
Pro Glu Lys Val Asn Ser Arg Asp Thr Ala Gly Arg Lys Ser Thr Pro
50 55 60
Leu His Phe Ala Ala Gly Phe Gly Arg Lys Asp Val Val Glu Tyr Leu
65 70 75 80
Leu Gln Asn Gly Ala Asn Val Gln Ala Arg Asp Asp Gly Gly Leu Ile
85 90 95
Pro Leu His Asn Ala Cys Ser Phe Gly His Ala Glu Val Val Asn Leu
100 105 110
Leu Leu Arg His Gly Ala Asp Pro Asn Ala Arg Asp Asn Trp Asn Tyr
115 120 125
Thr Pro Leu His Glu Ala Ala Ile Lys Gly Lys Ile Asp Val Cys Ile
130 135 140
Val Leu Leu Gln His Gly Ala Glu Pro Thr Ile Arg Asn Thr Asp Gly
145 150 155 160
Arg Thr Ala Leu Asp Leu Ala Asp Pro Ser Ala Lys Ala Val Leu Thr
165 170 175
Gly Glu Tyr Lys Lys Asp Glu Leu Leu Glu Ser Ala Arg Ser Gly Asn
180 185 190

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Glu Glu Lys Met Met Ala Leu Leu Thr Pro Leu Asn Val Asn Cys His
 195 200 205
 Ala Ser Asp Gly Arg Lys Ser Thr Pro Leu His Leu Ala Ala Gly Tyr
 210 215 220
 Asn Arg Val Lys Ile Val Gln Leu Leu Leu Gln His Gly Ala Asp Val
 225 230 235 240
 His Ala Lys Asp Lys Gly Asp Leu Val Pro Leu His Asn Ala Cys Ser
 245 250 255
 Tyr Gly His Tyr Glu Val Thr Glu Leu Leu Val Lys His Gly Ala Cys
 260 265 270
 Val Asn Ala Met Asp Leu Trp Gln Phe Thr Pro Leu His Glu Ala Ala
 275 280 285
 Ser Lys Asn Arg Val Glu Val Cys Ser Leu Leu Leu Ser Tyr Gly Ala
 290 295 300
 Asp Pro Thr Leu Leu Asn Cys His Asn Lys Ser Ala Ile Asp Leu Ala
 305 310 315 320
 Pro Thr Pro Gln Leu Lys Glu Arg Leu Ala Tyr Glu Phe Lys Gly His
 325 330 335
 Ser Leu Leu Gln Ala Ala Arg Glu Ala Asp Val Thr Arg Ile Lys Lys
 340 345 350
 His Leu Ser Leu Glu Met Val Asn Phe Lys His Pro Gln Thr His Glu
 355 360 365
 Thr Ala Leu His Cys Ala Ala Ala Ser Pro Tyr Pro Lys Arg Lys Gln
 370 375 380
 Ile Cys Glu Leu Leu Leu Arg Lys Gly Ala Asn Ile Asn Glu Lys Thr
 385 390 395 400
 Lys Glu Phe Leu Thr Pro Leu His Val Ala Ser Glu Lys Ala His Asn
 405 410 415
 Asp Val Val Glu Val Val Val Lys His Glu Ala Lys Val Asn Ala Leu
 420 425 430
 Asp Asn Leu Gly Gln Thr Ser Leu His Arg Ala Ala Tyr Cys Gly His
 435 440 445
 Leu Gln Thr Cys Arg Leu Leu Leu Ser Tyr Gly Cys Asp Pro Asn Ile
 450 455 460
 Ile Ser Leu Gln Gly Phe Thr Ala Leu Gln Met Gly Asn Glu Asn Val
 465 470 475 480
 Gln Gln Leu Leu Gln Glu Gly Ile Ser Leu Gly Asn Ser Glu Ala Asp
 485 490 495
 Arg Gln Leu Leu Glu Ala Ala Lys Ala Gly Asp Val Glu Thr Val Lys
 500 505 510
 Lys Leu Cys Thr Val Gln Ser Val Asn Cys
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<212> DNA

<213> Homo sapiens

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gcg agc gcc gcg gcc gag gcc gtg gag ccg gcc gcc cga gag ctg ttc 97
Ala Ser Ala Ala Ala Glu Ala Val Glu Pro Ala Ala Arg Glu Leu Phe
                20             25             30

gag gcg tgc cgc aac ggg gac gtg gaa cga gtc aag agg ctg gtg acg 145
Glu Ala Cys Arg Asn Gly Asp Val Glu Arg Val Lys Arg Leu Val Thr
                35             40             45

cct gag aag gtg aac agc cgc gac acg gcg ggc agg aaa tcc acc ccg 193
Pro Glu Lys Val Asn Ser Arg Asp Thr Ala Gly Arg Lys Ser Thr Pro
                50             55             60

ctg cac ttc gcc gca ggt ttt ggg cgg aaa gac gta gtt gaa tat ttg 241
Leu His Phe Ala Ala Gly Phe Gly Arg Lys Asp Val Val Glu Tyr Leu
  65             70             75             80

ctt cag aat ggt gca aat gtc caa gca cgt gat gat ggg ggc ctt att 289
Leu Gln Asn Gly Ala Asn Val Gln Ala Arg Asp Asp Gly Gly Leu Ile
                85             90             95

cct ctt cat aat gca tgc tct ttt ggt cat gct gaa gta gtc aat ctc 337
Pro Leu His Asn Ala Cys Ser Phe Gly His Ala Glu Val Val Asn Leu
                100             105             110

ctt ttg cga cat ggt gca gac ccc aat gct cga gat aat tgg aat tat 385
Leu Leu Arg His Gly Ala Asp Pro Asn Ala Arg Asp Asn Trp Asn Tyr
                115             120             125

act cct ctc cat gaa gct gca att aaa gga aag att gat gtt tgc att 433
Thr Pro Leu His Glu Ala Ala Ile Lys Gly Lys Ile Asp Val Cys Ile
                130             135             140

gtg ctg tta cag cat gga gct gag cca acc atc cga aat aca gat gga 481
Val Leu Leu Gln His Gly Ala Glu Pro Thr Ile Arg Asn Thr Asp Gly
  145             150             155             160

agg aca gca ttg gat tta gca gat cca tct gcc aaa gca gtg ctt act 529
Arg Thr Ala Leu Asp Leu Ala Asp Pro Ser Ala Lys Ala Val Leu Thr
                165             170             175

ggt gaa tat aag aaa gat gaa ctc tta gaa agt gcc agg agt ggc aat 577
Gly Glu Tyr Lys Lys Asp Glu Leu Leu Glu Ser Ala Arg Ser Gly Asn
                180             185             190

gaa gaa aaa atg atg gct cta ctc aca cca tta aat gtc aac tgc cac 625
Glu Glu Lys Met Met Ala Leu Leu Thr Pro Leu Asn Val Asn Cys His
                195             200             205

gca agt gat ggc aga aag tca act cca tta cat ttg gca gca gga tat 673
Ala Ser Asp Gly Arg Lys Ser Thr Pro Leu His Leu Ala Ala Gly Tyr
                210             215             220

aac aga gta aag att gta cag ctg tta ctg caa cat gga gct gat gtc 721
Asn Arg Val Lys Ile Val Gln Leu Leu Leu Gln His Gly Ala Asp Val
  225             230             235             240

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cat gct aaa gat aaa ggt gat ctg gta cca tta cac aat gcc tgt tct	769
His Ala Lys Asp Lys Gly Asp Leu Val Pro Leu His Asn Ala Cys Ser	
245 250 255	
tat ggt cat tat gaa gta act gaa ctt ttg gtc aag cat ggt gcc tgt	817
Tyr Gly His Tyr Glu Val Thr Glu Leu Val Lys His Gly Ala Cys	
260 265 270	
gta aat gca atg gac ttg tgg caa ttc act cct ctt cat gag gca gct	865
Val Asn Ala Met Asp Leu Trp Gln Phe Thr Pro Leu His Glu Ala Ala	
275 280 285	
tct aag aac agg gtt gaa gta tgt tct ctt ctc tta agt tat ggt gca	913
Ser Lys Asn Arg Val Glu Val Cys Ser Leu Leu Ser Tyr Gly Ala	
290 295 300	
gac cca aca ctg ctc aat tgt cac aat aaa agt gct ata gac ttg gct	961
Asp Pro Thr Leu Asn Cys His Asn Lys Ser Ala Ile Asp Leu Ala	
305 310 315 320	
ccc aca cca cag tta aaa gaa aga tta gca tat gaa ttt aaa ggc cac	1009
Pro Thr Pro Gln Leu Lys Glu Arg Leu Ala Tyr Glu Phe Lys Gly His	
325 330 335	
tcg ttg ctg caa gct gca cga gaa gct gat gtt act cga atc aaa aaa	1057
Ser Leu Leu Gln Ala Ala Arg Glu Ala Asp Val Thr Arg Ile Lys Lys	
340 345 350	
cat ctc tct ctg gaa atg gtg aat ttc aag cat cct caa aca cat gaa	1105
His Leu Ser Leu Glu Met Val Asn Phe Lys His Pro Gln Thr His Glu	
355 360 365	
aca gca ttg cat tgt gct gct gca tct cca tat ccc aaa aga aag caa	1153
Thr Ala Leu His Cys Ala Ala Ala Ser Pro Tyr Pro Lys Arg Lys Gln	
370 375 380	
ata tgt gaa ctg ttg cta aga aaa gga gca aac atc aat gaa aag act	1201
Ile Cys Glu Leu Leu Leu Arg Lys Gly Ala Asn Ile Asn Glu Lys Thr	
385 390 395 400	
aaa gaa ttc ttg act cct ctg cac gtg gca tct gag aaa gct cat aat	1249
Lys Glu Phe Leu Thr Pro Leu His Val Ala Ser Glu Lys Ala His Asn	
405 410 415	
gat gtt gtt gaa gta gtg gtg aaa cat gaa gca aag gtt aat gct ctg	1297
Asp Val Val Val Val Val Lys His Glu Ala Lys Val Asn Ala Leu	
420 425 430	
gat aat ctt ggt cag act tct cta cac aga gct gca tat tgt ggt cat	1345
Asp Asn Leu Gly Gln Thr Ser Leu His Arg Ala Ala Tyr Cys Gly His	
435 440 445	
cta caa acc tgc cgc cta ctc ctg agc tat ggg tgt gat cct aac att	1393
Leu Gln Thr Cys Arg Leu Leu Leu Ser Tyr Gly Cys Asp Pro Asn Ile	
450 455 460	
ata tcc ctt cag ggc ttt act gct tta cag atg gga aat gaa aat gta	1441
Ile Ser Leu Gln Gly Phe Thr Ala Leu Gln Met Gly Asn Glu Asn Val	
465 470 475 480	
cag caa ctc ctc caa gag ggt atc tca tta ggt aat tca gag gca gac	1489
Gln Gln Leu Leu Gln Glu Gly Ile Ser Leu Gly Asn Ser Glu Ala Asp	
485 490 495	
aga caa ttg ctg gaa gct gca aag gct gga gat gtc gaa act gta aaa	1537
Arg Gln Leu Leu Glu Ala Ala Lys Ala Gly Asp Val Glu Thr Val Lys	
500 505 510	

-56-

aaa ctg tgt act gtt cag agt gtc aac tgc aga gac att gaa ggg cgt	1585
Lys Leu Cys Thr Val Gln Ser Val Asn Cys Arg Asp Ile Glu Gly Arg	
515 520 525	
cag tct aca cca ctt cat ttt gca gct ggg tat aac aga gtg tcc gtg	1633
Gln Ser Thr Pro Leu His Phe Ala Ala Gly Tyr Asn Arg Val Ser Val	
530 535 540	
gtg gaa tat ctg cta cag cat gga gct gat gtg cat gct aaa gat aaa	1681
Val Glu Tyr Leu Leu Gln His Gly Ala Asp Val His Ala Lys Asp Lys	
545 550 555 560	
gga ggc ctt gta cct ttg cac aat gca tgt tct tat gga cat tat gaa	1729
Gly Gly Leu Val Pro Leu His Asn Ala Cys Ser Tyr Gly His Tyr Glu	
565 570 575	
gtt gca gaa ctt ctt gtt aaa cat gga gca gta gtt aat gta gct gat	1777
Val Ala Glu Leu Leu Val Lys His Gly Ala Val Val Asn Val Ala Asp	
580 585 590	
tta tgg aaa ttt aca cct tta cat gaa gca gca gca aaa gga aaa tat	1825
Leu Trp Lys Phe Thr Pro Leu His Glu Ala Ala Ala Lys Gly Lys Tyr	
595 600 605	
gaa att tgc aaa ctt ctg ctc cag cat ggt gca gac cct aca aaa aaa	1873
Glu Ile Cys Lys Leu Leu Leu Gln His Gly Ala Asp Pro Thr Lys Lys	
610 615 620	
aac agg gat gga aat act cct ttg gat ctt gtt aaa gat gga gat aca	1921
Asn Arg Asp Gly Asn Thr Pro Leu Asp Leu Val Lys Asp Gly Asp Thr	
625 630 635 640	
gat att caa gat ctg ctt agg gga gat gca gct ttg cta gat gct gcc	1969
Asp Ile Gln Asp Leu Leu Arg Gly Asp Ala Ala Leu Leu Asp Ala Ala	
645 650 655	
aag aag ggt tgt tta gcc aga gtg aag aag ttg tct tct cct gat aat	2017
Lys Lys Gly Cys Leu Ala Arg Val Lys Lys Leu Ser Ser Pro Asp Asn	
660 665 670	
gta aat tgc cgc gat acc caa ggc aga cat tca aca cct tta cat tta	2065
Val Asn Cys Arg Asp Thr Gln Gly Arg His Ser Thr Pro Leu His Leu	
675 680 685	
gca gct ggt tat aat aat tta gaa gtt gca gag tat ttg tta caa cac	2113
Ala Ala Gly Tyr Asn Asn Leu Glu Val Ala Glu Tyr Leu Leu Gln His	
690 695 700	
gga gct gat gtg aat gcc caa gac aaa gga gga ctt att cct tta cat	2161
Gly Ala Asp Val Asn Ala Gln Asp Lys Gly Gly Leu Ile Pro Leu His	
705 710 715 720	
aat gca gca tct tac ggg cat gta gat gta gca gct cta cta ata aag	2209
Asn Ala Ala Ser Tyr Gly His Val Asp Val Ala Ala Leu Leu Ile Lys	
725 730 735	
tat aat gca tgt gtc aat gcc acg gac aaa tgg gct ttc aca cct ttg	2257
Tyr Asn Ala Cys Val Asn Ala Thr Asp Lys Trp Ala Phe Thr Pro Leu	
740 745 750	
cac gaa gca gcc caa aag gga cga aca cag ctt tgt gct ttg ttg cta	2305
His Glu Ala Ala Gln Lys Gly Arg Thr Gln Leu Cys Ala Leu Leu Leu	
755 760 765	
gcc cat gga gct gac ccg act ctt aaa aat cag gaa gga caa aca cct	2353
Ala His Gly Ala Asp Pro Thr Leu Lys Asn Gln Glu Gly Gln Thr Pro	
770 775 780	

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tta gat tta gtt tca gca gat gat gtc agc gct ctt ctg aca gca gcc	2401
Leu Asp Leu Val Ser Ala Asp Asp Val Ser Ala Leu Leu Thr Ala Ala	
785 790 795 800	
atg ccc cca tct gct ctg ccc tct tgt tac aag cct caa gtg ctc aat	2449
Met Pro Pro Ser Ala Leu Pro Ser Cys Tyr Lys Pro Gln Val Leu Asn	
805 810 815	
ggg gtg aga agc cca gga gcc act gca gat gct ctc tct tca ggt cca	2497
Gly Val Arg Ser Pro Gly Ala Thr Ala Asp Ala Leu Ser Ser Gly Pro	
820 825 830	
tct agc cca tca agc ctt tct gca gcc agc agt ctt gac aac tta tct	2545
Ser Ser Ser Ser Leu Ser Ala Ser Ser Leu Asp Asn Leu Ser	
835 840 845	
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Gly Ser Phe Ser Glu Leu Ser Ser Val Val Ser Ser Ser Gly Thr Glu	
850 855 860	
ggg gct tcc agt ttg gag aaa aag gag gtt cca gga gta gat ttt agc	2641
Gly Ala Ser Ser Leu Glu Lys Lys Glu Val Pro Gly Val Asp Phe Ser	
865 870 875 880	
ata act caa ttc gta agg aat ctt gga ctt gag cac cta atg gat ata	2689
Ile Thr Gln Phe Val Arg Asn Leu Gly Leu Glu His Leu Met Asp Ile	
885 890 895	
ttt gag aga gaa cag atc act ttg gat gta tta gtt gag atg ggg cac	2737
Phe Glu Arg Glu Gln Ile Thr Leu Asp Val Leu Val Glu Met Gly His	
900 905 910	
aag gag ctg aag gag att gga atc aat gct tat gga cat agg cac aaa	2785
Lys Glu Leu Lys Glu Ile Gly Ile Asn Ala Tyr Gly His Arg His Lys	
915 920 925	
cta att aaa gga gtc gag aga ctt atc tcc gga caa caa ggt ctt aac	2833
Leu Ile Lys Gly Val Glu Arg Leu Ile Ser Gly Gln Gln Gly Leu Asn	
930 935 940	
cca tat tta act ttg aac acc tct ggt agt gga aca att ctt ata gat	2881
Pro Tyr Leu Thr Leu Asn Thr Ser Gly Ser Gly Thr Ile Leu Ile Asp	
945 950 955 960	
ctg tct cct gat gat aaa gag ttt cag tct gtg gag gaa gag atg caa	2929
Leu Ser Pro Asp Lys Glu Phe Gln Ser Val Glu Glu Glu Met Gln	
965 970 975	
agt aca gtt cga gag cac aga gat gga ggt cat gca ggt gga atc ttc	2977
Ser Thr Val Arg Glu His Arg Asp Gly Gly His Ala Gly Gly Ile Phe	
980 985 990	
aac aga tac aat att ctc aag att cag aag gtt tgt aac aag aaa cta	3025
Asn Arg Tyr Asn Ile Leu Lys Ile Gln Lys Val Cys Asn Lys Lys Leu	
995 1000 1005	
tgg gaa aga tac act cac cgg aga aaa gaa gtt tct gaa gaa aac cac	3073
Trp Glu Arg Tyr Thr His Arg Arg Lys Glu Val Ser Glu Glu Asn His	
1010 1015 1020	
aac cat gcc aat gaa cga atg cta ttt cat ggg tct cct ttt gtg aat	3121
Asn His Ala Asn Glu Arg Met Leu Phe His Gly Ser Pro Phe Val Asn	
1025 1030 1035 1040	
gca att atc cac aaa ggc ttt gat gaa agg cat gcg tac ata ggt ggt	3169
Ala Ile Ile His Lys Gly Phe Asp Glu Arg His Ala Tyr Ile Gly Gly	
1045 1050 1055	

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atg ttt gga gct ggc att tat ttt gct gaa aac tct tcc aaa agc aat 3217
Met Phe Gly Ala Gly Ile Tyr Phe Ala Glu Asn Ser Ser Lys Ser Asn
      1060      1065      1070

caa tat gta tat gga att gga gga ggt act ggg tgt cca gtt cac aaa 3265
Gln Tyr Val Tyr Gly Ile Gly Gly Gly Thr Gly Cys Pro Val His Lys
      1075      1080      1085

gac aga tct tgt tac att tgc cac agg cag ctg ctc ttt tgc cgg gta 3313
Asp Arg Ser Cys Tyr Ile Cys His Arg Gln Leu Phe Cys Arg Val
      1090      1095      1100

acc ttg gga aag tct ttc ctg cag ttc agt gca atg aaa atg gca cat 3361
Thr Leu Gly Lys Ser Phe Leu Gln Phe Ser Ala Met Lys Met Ala His
      1105      1110      1115      1120

tct cct cca ggt cat cac tca gtc act ggt agg ccc agt gta aat ggc 3409
Ser Pro Pro Gly His His Ser Val Thr Gly Arg Pro Ser Val Asn Gly
      1125      1130      1135

cta gca tta gct gaa tat gtt att tac aga gga gaa cag gct tat cct 3457
Leu Ala Leu Ala Glu Tyr Val Ile Tyr Arg Gly Glu Gln Ala Tyr Pro
      1140      1145      1150

gag tat tta att act tac cag att atg agg cct gaa ggt atg gtc gat 3505
Glu Tyr Leu Ile Thr Tyr Gln Ile Met Arg Pro Glu Gly Met Val Asp
      1155      1160      1165

gga taaatagtta ttttaagaaa ctaattccac tgaacctaaa atcatcaaag 3558
Gly

cagcagtggc ctctacgttt tactcctttg ctgaaaaaaa atcatcttgc ccacaggcct 3618

gtggcaaaaag gataaaaatg tgaacgaagt ttaacattct gacttgataa agctttaata 3678

atgtacagtg ttttctaatt atttcctgtt ttttcagcac tttaacagat gccattccag 3738

gttaaactgg gttgtctgta ctaaattata aacagagtta acttgaacct tttatatgtt 3798

atgcattgat tctaacaac tgtaatgccc tcaacagaac taattttact aatacaatac 3858

tgtgttcttt aaaacacagc atttacactg aatacaattt catttgtaaa actgtaaata 3918

agagcttttg tactagccca gtatttatit acattgcttt gtaatatataa tctgttttag 3978

aactgcagcg gtttacaaaa ttttttcata tgtattgttc atctatactt catcttacat 4038

cgatcatgatt gagtgatctt tacatttgat tccagaggct atgttcagtt gttagttggg 4098

aaagattgag ttatcagatt taatttgcc 4127

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  20           25           30

Glu Ala Cys Arg Asn Gly Asp Val Glu Arg Val Lys Arg Leu Val Thr
  35           40           45

Pro Glu Lys Val Asn Ser Arg Asp Thr Ala Gly Arg Lys Ser Thr Pro
  50           55           60

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Leu His Phe Ala Ala Gly Phe Gly Arg Lys Asp Val Val Glu Tyr Leu
 65 70 75 80
 Leu Gln Asn Gly Ala Asn Val Gln Ala Arg Asp Asp Gly Gly Leu Ile
 85 90 95
 Pro Leu His Asn Ala Cys Ser Phe Gly His Ala Glu Val Val Asn Leu
 100 105 110
 Leu Leu Arg His Gly Ala Asp Pro Asn Ala Arg Asp Asn Trp Asn Tyr
 115 120 125
 Thr Pro Leu His Glu Ala Ala Ile Lys Gly Lys Ile Asp Val Cys Ile
 130 135 140
 Val Leu Leu Gln His Gly Ala Glu Pro Thr Ile Arg Asn Thr Asp Gly
 145 150 155 160
 Arg Thr Ala Leu Asp Leu Ala Asp Pro Ser Ala Lys Ala Val Leu Thr
 165 170 175
 Gly Glu Tyr Lys Lys Asp Glu Leu Leu Glu Ser Ala Arg Ser Gly Asn
 180 185 190
 Glu Glu Lys Met Met Ala Leu Leu Thr Pro Leu Asn Val Asn Cys His
 195 200 205
 Ala Ser Asp Gly Arg Lys Ser Thr Pro Leu His Leu Ala Ala Gly Tyr
 210 215 220
 Asn Arg Val Lys Ile Val Gln Leu Leu Leu Gln His Gly Ala Asp Val
 225 230 235 240
 His Ala Lys Asp Lys Gly Asp Leu Val Pro Leu His Asn Ala Cys Ser
 245 250 255
 Tyr Gly His Tyr Glu Val Thr Glu Leu Leu Val Lys His Gly Ala Cys
 260 265 270
 Val Asn Ala Met Asp Leu Trp Gln Phe Thr Pro Leu His Glu Ala Ala
 275 280 285
 Ser Lys Asn Arg Val Glu Val Cys Ser Leu Leu Leu Ser Tyr Gly Ala
 290 295 300
 Asp Pro Thr Leu Leu Asn Cys His Asn Lys Ser Ala Ile Asp Leu Ala
 305 310 315 320
 Pro Thr Pro Gln Leu Lys Glu Arg Leu Ala Tyr Glu Phe Lys Gly His
 325 330 335
 Ser Leu Leu Gln Ala Ala Arg Glu Ala Asp Val Thr Arg Ile Lys Lys
 340 345 350
 His Leu Ser Leu Glu Met Val Asn Phe Lys His Pro Gln Thr His Glu
 355 360 365
 Thr Ala Leu His Cys Ala Ala Ala Ser Pro Tyr Pro Lys Arg Lys Gln
 370 375 380
 Ile Cys Glu Leu Leu Leu Arg Lys Gly Ala Asn Ile Asn Glu Lys Thr
 385 390 395 400
 Lys Glu Phe Leu Thr Pro Leu His Val Ala Ser Glu Lys Ala His Asn
 405 410 415
 Asp Val Val Glu Val Val Val Lys His Glu Ala Lys Val Asn Ala Leu
 420 425 430

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Asp Asn Leu Gly Gln Thr Ser Leu His Arg Ala Ala Tyr Cys Gly His
 435 440 445
 Leu Gln Thr Cys Arg Leu Leu Leu Ser Tyr Gly Cys Asp Pro Asn Ile
 450 455 460
 Ile Ser Leu Gln Gly Phe Thr Ala Leu Gln Met Gly Asn Glu Asn Val
 465 470 475 480
 Gln Gln Leu Leu Gln Glu Gly Ile Ser Leu Gly Asn Ser Glu Ala Asp
 485 490 495
 Arg Gln Leu Leu Glu Ala Ala Lys Ala Gly Asp Val Glu Thr Val Lys
 500 505 510
 Lys Leu Cys Thr Val Gln Ser Val Asn Cys Arg Asp Ile Glu Gly Arg
 515 520 525
 Gln Ser Thr Pro Leu His Phe Ala Ala Gly Tyr Asn Arg Val Ser Val
 530 535 540
 Val Glu Tyr Leu Leu Gln His Gly Ala Asp Val His Ala Lys Asp Lys
 545 550 555 560
 Gly Gly Leu Val Pro Leu His Asn Ala Cys Ser Tyr Gly His Tyr Glu
 565 570 575
 Val Ala Glu Leu Leu Val Lys His Gly Ala Val Val Asn Val Ala Asp
 580 585 590
 Leu Trp Lys Phe Thr Pro Leu His Glu Ala Ala Ala Lys Gly Lys Tyr
 595 600 605
 Glu Ile Cys Lys Leu Leu Leu Gln His Gly Ala Asp Pro Thr Lys Lys
 610 615 620
 Asn Arg Asp Gly Asn Thr Pro Leu Asp Leu Val Lys Asp Gly Asp Thr
 625 630 635 640
 Asp Ile Gln Asp Leu Leu Arg Gly Asp Ala Ala Leu Leu Asp Ala Ala
 645 650 655
 Lys Lys Gly Cys Leu Ala Arg Val Lys Lys Leu Ser Ser Pro Asp Asn
 660 665 670
 Val Asn Cys Arg Asp Thr Gln Gly Arg His Ser Thr Pro Leu His Leu
 675 680 685
 Ala Ala Gly Tyr Asn Asn Leu Glu Val Ala Glu Tyr Leu Leu Gln His
 690 695 700
 Gly Ala Asp Val Asn Ala Gln Asp Lys Gly Gly Leu Ile Pro Leu His
 705 710 715 720
 Asn Ala Ala Ser Tyr Gly His Val Asp Val Ala Ala Leu Leu Ile Lys
 725 730 735
 Tyr Asn Ala Cys Val Asn Ala Thr Asp Lys Trp Ala Phe Thr Pro Leu
 740 745 750
 His Glu Ala Ala Gln Lys Gly Arg Thr Gln Leu Cys Ala Leu Leu Leu
 755 760 765
 Ala His Gly Ala Asp Pro Thr Leu Lys Asn Gln Glu Gly Gln Thr Pro
 770 775 780
 Leu Asp Leu Val Ser Ala Asp Asp Val Ser Ala Leu Leu Thr Ala Ala
 785 790 795 800

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Met Pro Pro Ser Ala Leu Pro Ser Cys Tyr Lys Pro Gln Val Leu Asn
 805 810 815
 Gly Val Arg Ser Pro Gly Ala Thr Ala Asp Ala Leu Ser Ser Gly Pro
 820 825 830
 Ser Ser Pro Ser Ser Leu Ser Ala Ala Ser Ser Leu Asp Asn Leu Ser
 835 840 845
 Gly Ser Phe Ser Glu Leu Ser Ser Val Val Ser Ser Ser Gly Thr Glu
 850 855 860
 Gly Ala Ser Ser Leu Glu Lys Lys Glu Val Pro Gly Val Asp Phe Ser
 865 870 875 880
 Ile Thr Gln Phe Val Arg Asn Leu Gly Leu Glu His Leu Met Asp Ile
 885 890 895
 Phe Glu Arg Glu Gln Ile Thr Leu Asp Val Leu Val Glu Met Gly His
 900 905 910
 Lys Glu Leu Lys Glu Ile Gly Ile Asn Ala Tyr Gly His Arg His Lys
 915 920 925
 Leu Ile Lys Gly Val Glu Arg Leu Ile Ser Gly Gln Gln Gly Leu Asn
 930 935 940
 Pro Tyr Leu Thr Leu Asn Thr Ser Gly Ser Gly Thr Ile Leu Ile Asp
 945 950 955 960
 Leu Ser Pro Asp Asp Lys Glu Phe Gln Ser Val Glu Glu Glu Met Gln
 965 970 975
 Ser Thr Val Arg Glu His Arg Asp Gly Gly His Ala Gly Gly Ile Phe
 980 985 990
 Asn Arg Tyr Asn Ile Leu Lys Ile Gln Lys Val Cys Asn Lys Lys Leu
 995 1000 1005
 Trp Glu Arg Tyr Thr His Arg Arg Lys Glu Val Ser Glu Glu Asn His
 1010 1015 1020
 Asn His Ala Asn Glu Arg Met Leu Phe His Gly Ser Pro Phe Val Asn
 1025 1030 1035 1040
 Ala Ile Ile His Lys Gly Phe Asp Glu Arg His Ala Tyr Ile Gly Gly
 1045 1050 1055
 Met Phe Gly Ala Gly Ile Tyr Phe Ala Glu Asn Ser Ser Lys Ser Asn
 1060 1065 1070
 Gln Tyr Val Tyr Gly Ile Gly Gly Thr Gly Cys Pro Val His Lys
 1075 1080 1085
 Asp Arg Ser Cys Tyr Ile Cys His Arg Gln Leu Leu Phe Cys Arg Val
 1090 1095 1100
 Thr Leu Gly Lys Ser Phe Leu Gln Phe Ser Ala Met Lys Met Ala His
 1105 1110 1115 1120
 Ser Pro Pro Gly His His Ser Val Thr Gly Arg Pro Ser Val Asn Gly
 1125 1130 1135
 Leu Ala Leu Ala Glu Tyr Val Ile Tyr Arg Gly Glu Gln Ala Tyr Pro
 1140 1145 1150
 Glu Tyr Leu Ile Thr Tyr Gln Ile Met Arg Pro Glu Gly Met Val Asp
 1155 1160 1165
 Gly

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<210> 102
 <211> 32
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:Primer

<400> 102
 gagcattggg gtctgcacca tgcgcaaaa gg 32

<210> 103
 <211> 27
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:Primer

<400> 103
 ccataccta atagggc 27

<210> 104
 <211> 647
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (2)..(646)

<400> 104
 g gag ctg gca gga ggg gcc ttg cca gct tcc gcc gcc gcg tcg ttt cag 49
 Glu Leu Ala Gly Gly Ala Leu Pro Ala Ser Ala Ala Ala Ser Phe Gln
 1 5 10 15
 gac ccg gac ggc gga ttc gcg ctg cct ccg ccg ccg ccg ggc agc cgg 97
 Asp Pro Asp Gly Gly Phe Ala Leu Pro Pro Pro Pro Arg Gly Ser Arg
 20 25 30
 ggg gca ggg agc cca gcg agg ggc gcg cgt ggg cgc ggc cat ggg act 145
 Gly Ala Gly Ser Pro Ala Arg Gly Ala Arg Gly Arg Gly His Gly Thr
 35 40 45
 gcg ccg gat ccg gtg aca gca ggg agc caa gcg gcc ccg gcc ctg agc 193
 Ala Pro Asp Pro Val Thr Ala Gly Ser Gln Ala Ala Arg Ala Leu Ser
 50 55 60
 gcg tct tct ccg ggg ggc ctc gcc ctc ctg ctc gcg ggg ccg ggg ctc 241
 Ala Ser Ser Pro Gly Gly Leu Ala Leu Leu Leu Ala Gly Pro Gly Leu
 65 70 75 80
 ctg ctc cgg ttg ctg gcg ctg ttg ctg gct gtg gcg gcg gcc agg atc 289
 Leu Leu Arg Leu Ala Ala Leu Leu Leu Ala Val Ala Ala Arg Ile
 85 90 95
 atg tcg ggt cgc cgc tgc gcc ggc ggg gga gcg gcc tgc gcg agc gcc 337
 Met Ser Gly Arg Arg Cys Ala Gly Gly Ala Ala Cys Ala Ser Ala
 100 105 110
 gcg gcc gag gcc gtg gag ccg gcc gcc cga gag ctg ttc gag gcg tgc 385
 Ala Ala Glu Ala Val Glu Pro Ala Ala Arg Glu Leu Phe Glu Ala Cys
 115 120 125

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cgc aac ggg gac gtg gaa cga gtc aag agg ctg gtg acg cct gag aag 433
 Arg Asn Gly Asp Val Glu Arg Val Lys Arg Leu Val Thr Pro Glu Lys
 130 135 140

gtg aac agc cgc gac acg gcg ggc agg aaa tcc acc ccg ctg cac ttc 481
 Val Asn Ser Arg Asp Thr Ala Gly Arg Lys Ser Thr Pro Leu His Phe
 145 150 155 160

gcc gca ggt ttt ggg cgg aaa gac gta gtt gaa tat ttg ctt cag aat 529
 Ala Ala Gly Phe Gly Arg Lys Asp Val Val Glu Tyr Leu Leu Gln Asn
 165 170 175

ggt gca aat gtc caa gca cgt gat gat ggg ggc ctt att cct ctt cat 577
 Gly Ala Asn Val Gln Ala Arg Asp Asp Gly Gly Leu Ile Pro Leu His
 180 185 190

aat gca tgc tct ttt ggt cat gct gaa gta gtc aat ctc ctt ttg cga 625
 Asn Ala Cys Ser Phe Gly His Ala Glu Val Val Asn Leu Leu Leu Arg
 195 200 205

cat ggt gca gac ccc aat gct c 647
 His Gly Ala Asp Pro Asn Ala
 210 215

<210> 105

<211> 215

<212> PRT

<213> Homo sapiens

<400> 105

Glu Leu Ala Gly Gly Ala Leu Pro Ala Ser Ala Ala Ala Ser Phe Gln
 1 5 10 15

Asp Pro Asp Gly Gly Phe Ala Leu Pro Pro Pro Pro Arg Gly Ser Arg
 20 25 30

Gly Ala Gly Ser Pro Ala Arg Gly Ala Arg Gly Arg Gly His Gly Thr
 35 40 45

Ala Pro Asp Pro Val Thr Ala Gly Ser Gln Ala Ala Arg Ala Leu Ser
 50 55 60

Ala Ser Ser Pro Gly Gly Leu Ala Leu Leu Leu Ala Gly Pro Gly Leu
 65 70 75 80

Leu Leu Arg Leu Leu Ala Leu Leu Leu Ala Val Ala Ala Ala Arg Ile
 85 90 95

Met Ser Gly Arg Arg Cys Ala Gly Gly Gly Ala Ala Cys Ala Ser Ala
 100 105 110

Ala Ala Glu Ala Val Glu Pro Ala Ala Arg Glu Leu Phe Glu Ala Cys
 115 120 125

Arg Asn Gly Asp Val Glu Arg Val Lys Arg Leu Val Thr Pro Glu Lys
 130 135 140

Val Asn Ser Arg Asp Thr Ala Gly Arg Lys Ser Thr Pro Leu His Phe
 145 150 155 160

Ala Ala Gly Phe Gly Arg Lys Asp Val Val Glu Tyr Leu Leu Gln Asn
 165 170 175

Gly Ala Asn Val Gln Ala Arg Asp Asp Gly Gly Leu Ile Pro Leu His
 180 185 190

Asn Ala Cys Ser Phe Gly His Ala Glu Val Val Asn Leu Leu Leu Arg
 195 200 205

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His Gly Ala Asp Pro Asn Ala
210 215

<210> 106
<211> 4406
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (2)..(3787)

<400> 106
g gag ctg gca gga ggg gcc ttg cca gct tcc gcc gcc gcg tcg ttt cag 49
Glu Leu Ala Gly Gly Ala Leu Pro Ala Ser Ala Ala Ala Ser Phe Gln
1 5 10 15
gac ccg gac ggc gga ttc gcg ctg cct ccg ccg ccg ccg ggc agc ccg 97
Asp Pro Asp Gly Gly Phe Ala Leu Pro Pro Pro Pro Arg Gly Ser Arg
20 25 30
ggg gca ggg agc cca gcg agg ggc gcg cgt ggg cgc ggc cat ggg act 145
Gly Ala Gly Ser Pro Ala Arg Gly Ala Arg Gly Arg Gly His Gly Thr
35 40 45
gcg ccg gat ccg gtg aca gca ggg agc caa gcg gcc ccg gcc ctg agc 193
Ala Pro Asp Pro Val Thr Ala Gly Ser Gln Ala Ala Arg Ala Leu Ser
50 55 60
gcg tct tct ccg ggg ggc ctc gcc ctc ctg ctc gcg ggg ccg ggg ctc 241
Ala Ser Ser Pro Gly Gly Leu Ala Leu Leu Leu Ala Gly Pro Gly Leu
65 70 75 80
ctg ctc ccg ttg ctg gcg ctg ttg ctg gct gtg gcg gcg gcc agg atc 289
Leu Leu Arg Leu Leu Ala Leu Leu Leu Ala Val Ala Ala Ala Arg Ile
85 90 95
atg tcg ggt cgc cgc tgc gcc ggc ggg gga gcg gcc tgc gcg agc gcc 337
Met Ser Gly Arg Arg Cys Ala Gly Gly Gly Ala Ala Cys Ala Ser Ala
100 105 110
gcg gcc gag gcc gtg gag ccg gcc gcc cga gag ctg ttc gag gcg tgc 385
Ala Ala Glu Ala Val Glu Pro Ala Ala Arg Glu Leu Phe Glu Ala Cys
115 120 125
cgc aac ggg gac gtg gaa cga gtc aag agg ctg gtg acg cct gag aag 433
Arg Asn Gly Asp Val Glu Arg Val Lys Arg Leu Val Thr Pro Glu Lys
130 135 140
gtg aac agc cgc gac acg gcg ggc agg aaa tcc acc ccg ctg cac ttc 481
Val Asn Ser Arg Asp Thr Ala Gly Arg Lys Ser Thr Pro Leu His Phe
145 150 155 160
gcc gca ggt ttt ggg ccg aaa gac gta gtt gaa tat ttg ctt cag aat 529
Ala Ala Gly Phe Gly Arg Lys Asp Val Val Glu Tyr Leu Leu Gln Asn
165 170 175
ggg gca aat gtc caa gca cgt gat gat ggg ggc ctt att cct ctt cat 577
Gly Ala Asn Val Gln Ala Arg Asp Asp Gly Gly Leu Ile Pro Leu His
180 185 190
aat gca tgc tct ttt ggt cat gct gaa gta gtc aat ctc ctt ttg cga 625
Asn Ala Cys Ser Phe Gly His Ala Glu Val Val Asn Leu Leu Leu Arg
195 200 205
cat ggt gca gac ccc aat gct cga gat aat tgg aat tat act cct ctc 673
His Gly Ala Asp Pro Asn Ala Arg Asp Asn Trp Asn Tyr Thr Pro Leu
210 215 220

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cat gaa gct gca att aaa gga aag att gat gtt tgc att gtg ctg tta His Glu Ala Ala Ile Lys Gly Lys Ile Asp Val Cys Ile Val Leu Leu 225 230 235 240	721
cag cat gga gct gag cca acc atc cga aat aca gat gga agg aca gca Gln His Gly Ala Glu Pro Thr Ile Arg Asn Thr Asp Gly Arg Thr Ala 245 250 255	769
ttg gat tta gca gat cca tct gcc aaa gca gtg ctt act ggt gaa tat Leu Asp Leu Ala Asp Pro Ser Ala Lys Ala Val Leu Thr Gly Glu Tyr 260 265 270	817
aag aaa gat gaa ctc tta gaa agt gcc agg agt ggc aat gaa gaa aaa Lys Lys Asp Glu Leu Leu Glu Ser Ala Arg Ser Gly Asn Glu Glu Lys 275 280 285	865
atg atg gct cta ctc aca cca tta aat gtc aac tgc cac gca agt gat Met Met Ala Leu Leu Thr Pro Leu Asn Val Asn Cys His Ala Ser Asp 290 295 300	913
ggc aga aag tca act cca tta cat ttg gca gca gga tat aac aga gta Gly Arg Lys Ser Thr Pro Leu His Leu Ala Ala Gly Tyr Asn Arg Val 305 310 315 320	961
aag att gta cag ctg tta ctg caa cat gga gct gat gtc cat gct aaa Lys Ile Val Gln Leu Leu Leu Gln His Gly Ala Asp Val His Ala Lys 325 330 335	1009
gat aaa ggt gat ctg gta cca tta cac aat gcc tgt tct tat ggt cat Asp Lys Gly Asp Leu Val Pro Leu His Asn Ala Cys Ser Tyr Gly His 340 345 350	1057
tat gaa gta act gaa ctt ttg gtc aag cat ggt gcc tgt gta aat gca Tyr Glu Val Thr Glu Leu Leu Val Lys His Gly Ala Cys Val Asn Ala 355 360 365	1105
atg gac ttg tgg caa ttc act cct ctt cat gag gca gct tct aag aac Met Asp Leu Trp Gln Phe Thr Pro Leu His Glu Ala Ala Ser Lys Asn 370 375 380	1153
agg gtt gaa gta tgt tct ctt ctc tta agt tat ggt gca gac cca aca Arg Val Glu Val Cys Ser Leu Leu Leu Ser Tyr Gly Ala Asp Pro Thr 385 390 395 400	1201
ctg ctc aat tgt cac aat aaa agt gct ata gac ttg gct ccc aca cca Leu Leu Asn Cys His Asn Lys Ser Ala Ile Asp Leu Ala Pro Thr Pro 405 410 415	1249
cag tta aaa gaa aga tta gca tat gaa ttt aaa ggc cac tcg ttg ctg Gln Leu Lys Glu Arg Leu Ala Tyr Glu Phe Lys Gly His Ser Leu Leu 420 425 430	1297
caa gct gca cga gaa gct gat gtt act cga atc aaa aaa cat ctc tct Gln Ala Ala Arg Glu Ala Asp Val Thr Arg Ile Lys Lys His Leu Ser 435 440 445	1345
ctg gaa atg gtg aat ttc aag cat cct caa aca cat gaa aca gca ttg Leu Glu Met Val Asn Phe Lys His Pro Gln Thr His Glu Thr Ala Leu 450 455 460	1393
cat tgt gct gct gca tct cca tat ccc aaa aga aag caa ata tgt gaa His Cys Ala Ala Ala Ser Pro Tyr Pro Lys Arg Lys Gln Ile Cys Glu 465 470 475 480	1441
ctg ttg cta aga aaa gga gca aac atc aat gaa aag act aaa gaa ttc Leu Leu Leu Arg Lys Gly Ala Asn Ile Asn Glu Lys Thr Lys Glu Phe 485 490 495	1489

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ttg act cct ctg cac gtg gca tct gag aaa gct cat aat gat gtt gtt	1537
Leu Thr Pro Leu His Val Ala Ser Glu Lys Ala His Asn Asp Val Val	
500 505 510	
gaa gta gtg gtg aaa cat gaa gca aag gtt aat gct ctg gat aat ctt	1585
Glu Val Val Val Lys His Glu Ala Lys Val Asn Ala Leu Asp Asn Leu	
515 520 525	
ggg cag act tct cta cac aga gct gca tat tgt ggt cat cta caa acc	1633
Gly Gln Thr Ser Leu His Arg Ala Ala Tyr Cys Gly His Leu Gln Thr	
530 535 540	
tgc cgc cta ctc ctg agc tat ggg tgt gat cct aac att ata tcc ctt	1681
Cys Arg Leu Leu Leu Ser Tyr Gly Cys Asp Pro Asn Ile Ile Ser Leu	
545 550 555 560	
cag ggc ttt act gct tta cag atg gga aat gaa aat gta cag caa ctc	1729
Gln Gly Phe Thr Ala Leu Gln Met Gly Asn Glu Asn Val Gln Gln Leu	
565 570 575	
ctc caa gag ggt atc tca tta ggt aat tca gag gca gac aga caa ttg	1777
Leu Gln Glu Gly Ile Ser Leu Gly Asn Ser Glu Ala Asp Arg Gln Leu	
580 585 590	
ctg gaa gct gca aag gct gga gat gtc gaa act gta aaa aaa ctg tgt	1825
Leu Glu Ala Ala Lys Ala Gly Asp Val Glu Thr Val Lys Lys Leu Cys	
595 600 605	
act gtt cag agt gtc aac tgc aga gac att gaa ggg cgt cag tct aca	1873
Thr Val Gln Ser Val Asn Cys Arg Asp Ile Glu Gly Arg Gln Ser Thr	
610 615 620	
cca ctt cat ttt gca gct ggg tat aac aga gtg tcc gtg gtg gaa tat	1921
Pro Leu His Phe Ala Ala Gly Tyr Asn Arg Val Ser Val Val Glu Tyr	
625 630 635 640	
ctg cta cag cat gga gct gat gtg cat gct aaa gat aaa gga ggc ctt	1969
Leu Leu Gln His Gly Ala Asp Val His Ala Lys Asp Lys Gly Gly Leu	
645 650 655	
gta cct ttg cac aat gca tgt tct tat gga cat tat gaa gtt gca gaa	2017
Val Pro Leu His Asn Ala Cys Ser Tyr Gly His Tyr Glu Val Ala Glu	
660 665 670	
ctt ctt gtt aaa cat gga gca gta gtt aat gta gct gat tta tgg aaa	2065
Leu Leu Val Lys His Gly Ala Val Val Asn Val Ala Asp Leu Trp Lys	
675 680 685	
ttt aca cct tta cat gaa gca gca gca aaa gga aaa tat gaa att tgc	2113
Phe Thr Pro Leu His Glu Ala Ala Ala Lys Gly Lys Tyr Glu Ile Cys	
690 695 700	
aaa ctt ctg ctc cag cat ggt gca gac cct aca aaa aaa aac agg gat	2161
Lys Leu Leu Leu Gln His Gly Ala Asp Pro Thr Lys Lys Asn Arg Asp	
705 710 715 720	
gga aat act cct ttg gat ctt gtt aaa gat gga gat aca gat att caa	2209
Gly Asn Thr Pro Leu Asp Leu Val Lys Asp Gly Asp Thr Asp Ile Gln	
725 730 735	
gat ctg ctt agg gga gat gca gct ttg cta gat gct gcc aag aag ggt	2257
Asp Leu Leu Arg Gly Asp Ala Ala Leu Leu Asp Ala Ala Lys Lys Gly	
740 745 750	
tgt tta gcc aga gtg aag aag ttg tct tct cct gat aat gta aat tgc	2305
Cys Leu Ala Arg Val Lys Lys Leu Ser Ser Pro Asp Asn Val Asn Cys	
755 760 765	

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cgc gat acc caa ggc aga cat tca aca cct tta cat tta gca gct ggt	2353
Arg Asp Thr Gln Gly Arg His Ser Thr Pro Leu His Leu Ala Ala Gly	
770 775 780	
tat aat aat tta gaa gtt gca gag tat ttg tta caa cac gga gct gat	2401
Tyr Asn Asn Leu Glu Val Ala Glu Tyr Leu Ile Pro Leu His Gly Ala Asp	
785 790 795 800	
gtg aat gcc caa gac aaa gga gga ctt att cct tta cat aat gca gca	2449
Val Asn Ala Gln Asp Lys Gly Gly Leu Ile Pro Leu His Asn Ala Ala	
805 810 815	
tct tac ggg cat gta gat gta gca gct cta cta ata aag tat aat gca	2497
Ser Tyr Gly His Val Asp Val Ala Leu Leu Ile Lys Tyr Asn Ala	
820 825 830	
tgt gtc aat gcc acg gac aaa tgg gct ttc aca cct ttg cac gaa gca	2545
Cys Val Asn Ala Thr Asp Lys Trp Ala Phe Thr Pro Leu His Glu Ala	
835 840 845	
gcc caa aag gga cga aca cag ctt tgt gct ttg ttg cta gcc cat gga	2593
Ala Gln Lys Gly Arg Thr Gln Leu Cys Ala Leu Leu Leu Ala His Gly	
850 855 860	
gct gac ccg act ctt aaa aat cag gaa gga caa aca cct tta gat tta	2641
Ala Asp Pro Thr Leu Lys Asn Gln Glu Gly Gln Thr Pro Leu Asp Leu	
865 870 875 880	
gtt tca gca gat gat gtc agc gct ctt ctg aca gca gcc atg ccc cca	2689
Val Ser Ala Asp Asp Val Ser Ala Leu Leu Thr Ala Ala Met Pro Pro	
885 890 895	
tct gct ctg ccc tct tgt tac aag cct caa gtg ctc aat ggt gtg aga	2737
Ser Ala Leu Pro Ser Cys Tyr Lys Pro Gln Val Leu Asn Gly Val Arg	
900 905 910	
agc cca gga gcc act gca gat gct ctc tct tca ggt cca tct agc cca	2785
Ser Pro Gly Ala Thr Ala Asp Ala Leu Ser Ser Gly Pro Ser Ser Pro	
915 920 925	
tca agc ctt tct gca gcc agc agt ctt gac aac tta tct ggg agt ttt	2833
Ser Ser Leu Ser Ala Ala Ser Ser Leu Asp Asn Leu Ser Gly Ser Phe	
930 935 940	
tca gaa ctg tct tca gta gtt agt tca agt gga aca gag ggt gct tcc	2881
Ser Glu Leu Ser Ser Val Val Ser Ser Ser Gly Thr Glu Gly Ala Ser	
945 950 955 960	
agt ttg gag aaa aag gag gtt cca gga gta gat ttt agc ata act caa	2929
Ser Leu Glu Lys Lys Glu Val Pro Gly Val Asp Phe Ser Ile Thr Gln	
965 970 975	
ttc gta agg aat ctt gga ctt gag cac cta atg gat ata ttt gag aga	2977
Phe Val Arg Asn Leu Gly Leu Glu His Leu Met Asp Ile Phe Glu Arg	
980 985 990	
gaa cag atc act ttg gat gta tta gtt gag atg ggg cac aag gag ctg	3025
Glu Gln Ile Thr Leu Asp Val Leu Val Glu Met Gly His Lys Glu Leu	
995 1000 1005	
aag gag att gga atc aat gct tat gga cat agg cac aaa cta att aaa	3073
Lys Glu Ile Gly Ile Asn Ala Tyr Gly His Arg His Lys Leu Ile Lys	
1010 1015 1020	
gga gtc gag aga ctt atc tcc gga caa caa ggt ctt aac cca tat tta	3121
Gly Val Glu Arg Leu Ile Ser Gly Gln Gln Gly Leu Asn Pro Tyr Leu	
1025 1030 1035 1040	

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act ttg aac acc tct ggt agt gga aca att ctt ata gat ctg tct cct 3169
 Thr Leu Asn Thr Ser Gly Ser Gly Thr Ile Leu Ile Asp Leu Ser Pro
 1045 1050 1055

gat gat aaa gag ttt cag tct gtg gag gaa gag atg caa agt aca gtt 3217
 Asp Asp Lys Glu Phe Gln Ser Val Glu Glu Met Gln Ser Thr Val
 1060 1065 1070

cga gag cac aga gat gga ggt cat gca ggt gga atc ttc aac aga tac 3265
 Arg Glu His Arg Asp Gly Gly His Ala Gly Gly Ile Phe Asn Arg Tyr
 1075 1080 1085

aat att ctc aag att cag aag gtt tgt aac aag aaa cta tgg gaa aga 3313
 Asn Ile Leu Lys Ile Gln Lys Val Cys Asn Lys Lys Leu Trp Glu Arg
 1090 1095 1100

tac act cac cgg aga aaa gaa gtt tct gaa gaa aac cac aac cat gcc 3361
 Tyr Thr His Arg Arg Lys Glu Val Ser Glu Glu Asn His Asn His Ala
 1105 1110 1115 1120

aat gaa cga atg cta ttt cat ggg tct cct ttt gtg aat gca att atc 3409
 Asn Glu Arg Met Leu Phe His Gly Ser Pro Phe Val Asn Ala Ile Ile
 1125 1130 1135

cac aaa ggc ttt gat gaa agg cat gcg tac ata ggt ggt atg ttt gga 3457
 His Lys Gly Phe Asp Glu Arg His Ala Tyr Ile Gly Gly Met Phe Gly
 1140 1145 1150

gct ggc att tat ttt gct gaa aac tct tcc aaa agc aat caa tat gta 3505
 Ala Gly Ile Tyr Phe Ala Glu Asn Ser Ser Lys Ser Asn Gln Tyr Val
 1155 1160 1165

tat gga att gga gga ggt act ggg tgt cca gtt cac aaa gac aga tct 3553
 Tyr Gly Ile Gly Gly Gly Thr Gly Cys Pro Val His Lys Asp Arg Ser
 1170 1175 1180

tgt tac att tgc cac agg cag ctg ctc ttt tgc cgg gta acc ttg gga 3601
 Cys Tyr Ile Cys His Arg Gln Leu Leu Phe Cys Arg Val Thr Leu Gly
 1185 1190 1195 1200

aag tct ttc ctg cag ttc agt gca atg aaa atg gca cat tct cct cca 3649
 Lys Ser Phe Leu Gln Phe Ser Ala Met Lys Met Ala His Ser Pro Pro
 1205 1210 1215

ggt cat cac tca gtc act ggt agg ccc agt gta aat ggc cta gca tta 3697
 Gly His His Ser Val Thr Gly Arg Pro Ser Val Asn Gly Leu Ala Leu
 1220 1225 1230

gct gaa tat gtt att tac aga gga gaa cag gct tat cct gag tat tta 3745
 Ala Glu Tyr Val Ile Tyr Arg Gly Glu Gln Ala Tyr Pro Glu Tyr Leu
 1235 1240 1245

att act tac cag att atg agg cct gaa ggt atg gtc gat gga 3787
 Ile Thr Tyr Gln Ile Met Arg Pro Glu Gly Met Val Asp Gly
 1250 1255 1260

taaatagtta ttttaagaaa ctaattccac tgaacctaaa atcatcaaag cagcagtggc 3847

ctctacgttt tactcctttg ctgaaaaaaa atcatcttgc ccacaggcct gtggcaaaaag 3907

gataaaaatg tgaacgaagt ttaacattct gacttgataa agctttaata atgtacagtg 3967

tttttctaatt atttcctggt ttttcagcac ttttaacagat gccattccag gttaaaactgg 4027

gttgtctgta ctaaattata aacagagtta acttgaacct tttatatggt atgcattgat 4087

tctaacaac tgtaatgccc tcaacagaac taattttact aatacaatac tgtgttcttt 4147

aaaacacagc atttacactg aatacaattt catttgtaaa actgtaaata agagcttttg 4207

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tactagccca gtatttattt acattgcttt gtaataataa tctgttttag aactgcagcg 4267
 gtttacaaaa ttttttcata tgtattgttc atctatactt catcttacat cgtcatgatt 4327
 gagtgatctt tacatttgat tccagaggct atgttcagtt gttagtggg aaagattgag 4387
 ttatcagatt taatttgcc 4406

<210> 107

<211> 1262

<212> PRT

<213> Homo sapiens

<400> 107

Glu Leu Ala Gly Gly Ala Leu Pro Ala Ser Ala Ala Ala Ser Phe Gln
 1 5 10 15
 Asp Pro Asp Gly Gly Phe Ala Leu Pro Pro Pro Pro Arg Gly Ser Arg
 20 25 30
 Gly Ala Gly Ser Pro Ala Arg Gly Ala Arg Gly Arg Gly His Gly Thr
 35 40 45
 Ala Pro Asp Pro Val Thr Ala Gly Ser Gln Ala Ala Arg Ala Leu Ser
 50 55 60
 Ala Ser Ser Pro Gly Gly Leu Ala Leu Leu Leu Ala Gly Pro Gly Leu
 65 70 75 80
 Leu Leu Arg Leu Leu Ala Leu Leu Leu Ala Val Ala Ala Ala Arg Ile
 85 90 95
 Met Ser Gly Arg Arg Cys Ala Gly Gly Gly Ala Ala Cys Ala Ser Ala
 100 105 110
 Ala Ala Glu Ala Val Glu Pro Ala Ala Arg Glu Leu Phe Glu Ala Cys
 115 120 125
 Arg Asn Gly Asp Val Glu Arg Val Lys Arg Leu Val Thr Pro Glu Lys
 130 135 140
 Val Asn Ser Arg Asp Thr Ala Gly Arg Lys Ser Thr Pro Leu His Phe
 145 150 155 160
 Ala Ala Gly Phe Gly Arg Lys Asp Val Val Glu Tyr Leu Leu Gln Asn
 165 170 175
 Gly Ala Asn Val Gln Ala Arg Asp Asp Gly Gly Leu Ile Pro Leu His
 180 185 190
 Asn Ala Cys Ser Phe Gly His Ala Glu Val Val Asn Leu Leu Arg
 195 200 205
 His Gly Ala Asp Pro Asn Ala Arg Asp Asn Trp Asn Tyr Thr Pro Leu
 210 215 220
 His Glu Ala Ala Ile Lys Gly Lys Ile Asp Val Cys Ile Val Leu Leu
 225 230 235 240
 Gln His Gly Ala Glu Pro Thr Ile Arg Asn Thr Asp Gly Arg Thr Ala
 245 250 255
 Leu Asp Leu Ala Asp Pro Ser Ala Lys Ala Val Leu Thr Gly Glu Tyr
 260 265 270
 Lys Lys Asp Glu Leu Leu Glu Ser Ala Arg Ser Gly Asn Glu Glu Lys
 275 280 285

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Met Met Ala Leu Leu Thr Pro Leu Asn Val Asn Cys His Ala Ser Asp
 290 295 300
 Gly Arg Lys Ser Thr Pro Leu His Leu Ala Ala Gly Tyr Asn Arg Val
 305 310 315 320
 Lys Ile Val Gln Leu Leu Leu Gln His Gly Ala Asp Val His Ala Lys
 325 330 335
 Asp Lys Gly Asp Leu Val Pro Leu His Asn Ala Cys Ser Tyr Gly His
 340 345 350
 Tyr Glu Val Thr Glu Leu Leu Val Lys His Gly Ala Cys Val Asn Ala
 355 360 365
 Met Asp Leu Trp Gln Phe Thr Pro Leu His Glu Ala Ala Ser Lys Asn
 370 375 380
 Arg Val Glu Val Cys Ser Leu Leu Leu Ser Tyr Gly Ala Asp Pro Thr
 385 390 395 400
 Leu Leu Asn Cys His Asn Lys Ser Ala Ile Asp Leu Ala Pro Thr Pro
 405 410 415
 Gln Leu Lys Glu Arg Leu Ala Tyr Glu Phe Lys Gly His Ser Leu Leu
 420 425 430
 Gln Ala Ala Arg Glu Ala Asp Val Thr Arg Ile Lys Lys His Leu Ser
 435 440 445
 Leu Glu Met Val Asn Phe Lys His Pro Gln Thr His Glu Thr Ala Leu
 450 455 460
 His Cys Ala Ala Ala Ser Pro Tyr Pro Lys Arg Lys Gln Ile Cys Glu
 465 470 475 480
 Leu Leu Leu Arg Lys Gly Ala Asn Ile Asn Glu Lys Thr Lys Glu Phe
 485 490 495
 Leu Thr Pro Leu His Val Ala Ser Glu Lys Ala His Asn Asp Val Val
 500 505 510
 Glu Val Val Val Lys His Glu Ala Lys Val Asn Ala Leu Asp Asn Leu
 515 520 525
 Gly Gln Thr Ser Leu His Arg Ala Ala Tyr Cys Gly His Leu Gln Thr
 530 535 540
 Cys Arg Leu Leu Leu Ser Tyr Gly Cys Asp Pro Asn Ile Ile Ser Leu
 545 550 555 560
 Gln Gly Phe Thr Ala Leu Gln Met Gly Asn Glu Asn Val Gln Gln Leu
 565 570 575
 Leu Gln Glu Gly Ile Ser Leu Gly Asn Ser Glu Ala Asp Arg Gln Leu
 580 585 590
 Leu Glu Ala Ala Lys Ala Gly Asp Val Glu Thr Val Lys Lys Leu Cys
 595 600 605
 Thr Val Gln Ser Val Asn Cys Arg Asp Ile Glu Gly Arg Gln Ser Thr
 610 615 620
 Pro Leu His Phe Ala Ala Gly Tyr Asn Arg Val Ser Val Val Glu Tyr
 625 630 635 640
 Leu Leu Gln His Gly Ala Asp Val His Ala Lys Asp Lys Gly Gly Leu
 645 650 655

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Val Pro Leu His Asn Ala Cys Ser Tyr Gly His Tyr Glu Val Ala Glu
 660 665 670
 Leu Leu Val Lys His Gly Ala Val Val Asn Val Ala Asp Leu Trp Lys
 675 680 685
 Phe Thr Pro Leu His Glu Ala Ala Ala Lys Gly Lys Tyr Glu Ile Cys
 690 695 700
 Lys Leu Leu Leu Gln His Gly Ala Asp Pro Thr Lys Lys Asn Arg Asp
 705 710 715 720
 Gly Asn Thr Pro Leu Asp Leu Val Lys Asp Gly Asp Thr Asp Ile Gln
 725 730 735
 Asp Leu Leu Arg Gly Asp Ala Ala Leu Leu Asp Ala Ala Lys Lys Gly
 740 745 750
 Cys Leu Ala Arg Val Lys Lys Leu Ser Ser Pro Asp Asn Val Asn Cys
 755 760 765
 Arg Asp Thr Gln Gly Arg His Ser Thr Pro Leu His Leu Ala Ala Gly
 770 775 780
 Tyr Asn Asn Leu Glu Val Ala Glu Tyr Leu Leu Gln His Gly Ala Asp
 785 790 795 800
 Val Asn Ala Gln Asp Lys Gly Gly Leu Ile Pro Leu His Asn Ala Ala
 805 810 815
 Ser Tyr Gly His Val Asp Val Ala Ala Leu Leu Ile Lys Tyr Asn Ala
 820 825 830
 Cys Val Asn Ala Thr Asp Lys Trp Ala Phe Thr Pro Leu His Glu Ala
 835 840 845
 Ala Gln Lys Gly Arg Thr Gln Leu Cys Ala Leu Leu Leu Ala His Gly
 850 855 860
 Ala Asp Pro Thr Leu Lys Asn Gln Glu Gly Gln Thr Pro Leu Asp Leu
 865 870 875 880
 Val Ser Ala Asp Asp Val Ser Ala Leu Leu Thr Ala Ala Met Pro Pro
 885 890 895
 Ser Ala Leu Pro Ser Cys Tyr Lys Pro Gln Val Leu Asn Gly Val Arg
 900 905 910
 Ser Pro Gly Ala Thr Ala Asp Ala Leu Ser Ser Gly Pro Ser Ser Pro
 915 920 925
 Ser Ser Leu Ser Ala Ala Ser Ser Leu Asp Asn Leu Ser Gly Ser Phe
 930 935 940
 Ser Glu Leu Ser Ser Val Val Ser Ser Ser Gly Thr Glu Gly Ala Ser
 945 950 955 960
 Ser Leu Glu Lys Lys Glu Val Pro Gly Val Asp Phe Ser Ile Thr Gln
 965 970 975
 Phe Val Arg Asn Leu Gly Leu Glu His Leu Met Asp Ile Phe Glu Arg
 980 985 990
 Glu Gln Ile Thr Leu Asp Val Leu Val Glu Met Gly His Lys Glu Leu
 995 1000 1005
 Lys Glu Ile Gly Ile Asn Ala Tyr Gly His Arg His Lys Leu Ile Lys
 1010 1015 1020

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Gly Val Glu Arg Leu Ile Ser Gly Gln Gln Gly Leu Asn Pro Tyr Leu
 1025 1030 1035 1040
 Thr Leu Asn Thr Ser Gly Ser Gly Thr Ile Leu Ile Asp Leu Ser Pro
 1045 1050 1055
 Asp Asp Lys Glu Phe Gln Ser Val Glu Glu Glu Met Gln Ser Thr Val
 1060 1065 1070
 Arg Glu His Arg Asp Gly Gly His Ala Gly Gly Ile Phe Asn Arg Tyr
 1075 1080 1085
 Asn Ile Leu Lys Ile Gln Lys Val Cys Asn Lys Lys Leu Trp Glu Arg
 1090 1095 1100
 Tyr Thr His Arg Arg Lys Glu Val Ser Glu Glu Asn His Asn His Ala
 1105 1110 1115 1120
 Asn Glu Arg Met Leu Phe His Gly Ser Pro Phe Val Asn Ala Ile Ile
 1125 1130 1135
 His Lys Gly Phe Asp Glu Arg His Ala Tyr Ile Gly Gly Met Phe Gly
 1140 1145 1150
 Ala Gly Ile Tyr Phe Ala Glu Asn Ser Ser Lys Ser Asn Gln Tyr Val
 1155 1160 1165
 Tyr Gly Ile Gly Gly Gly Thr Gly Cys Pro Val His Lys Asp Arg Ser
 1170 1175 1180
 Cys Tyr Ile Cys His Arg Gln Leu Leu Phe Cys Arg Val Thr Leu Gly
 1185 1190 1195 1200
 Lys Ser Phe Leu Gln Phe Ser Ala Met Lys Met Ala His Ser Pro Pro
 1205 1210 1215
 Gly His His Ser Val Thr Gly Arg Pro Ser Val Asn Gly Leu Ala Leu
 1220 1225 1230
 Ala Glu Tyr Val Ile Tyr Arg Gly Glu Gln Ala Tyr Pro Glu Tyr Leu
 1235 1240 1245
 Ile Thr Tyr Gln Ile Met Arg Pro Glu Gly Met Val Asp Gly
 1250 1255 1260

<210> 108
 <211> 436
 <212> DNA
 <213> Homo sapiens

<400> 108
 ttttttttgc agttctaaaa cagattttata ttacaaagca atgtaaataa atactgggct 60
 agtacaaaag ctcttattta cagttttaca aatgaaattg tattcagtgt aaatgctgtg 120
 ttttaaagaa cacagtattg tattagtaaa attagttctg ttgagggcat tacagtttgt 180
 tagaatcaat gcataacata taaaagggtc aagttaactc tgtttataat ttagtacaga 240
 caaccagtt taacctggga tgggcatctg ttaaagtgt ggaaaaaaca gggaaatatt 300
 taggaaaaaca ctggtacatt atttaaaggc tttntccaag gtcaggantg tttaaacttc 360
 gtttcacatt tttatccttt tggccacggc ctgtggggcn aggatggatt tttttccgg 420
 ccaagggtgt taaacg 436

<210> 109
 <211> 21
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:Primer

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<400> 109
cgccctgagaa ggtgaacagc c 21

<210> 110
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 110
acgcctcgaa cagctctcgg 20

<210> 111
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 111
gcgtgggcgc ggccatggga ctg 23

<210> 112
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 112
cagcgcgaat ccgccgtccg 20

<210> 113
<211> 620
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (3)..(620)

<400> 113
tt aaa aca aca aca aca aaa aac aca ata tgc agg atc gtt cgg ctt 47
Lys Thr Thr Thr Thr Lys Asn Thr Ile Cys Arg Ile Val Arg Leu
1 5 10 15

cag cag aac cca ccg caa aga tgg cgg tgg gac gaa gcc cct tct ccc 95
Gln Gln Asn Pro Pro Gln Arg Trp Arg Trp Asp Glu Ala Pro Ser Pro
20 25 30

gcc gcc gaa gcc tct cgc ctc aca ttt ccc aca aac cct tcg cgc cgc 143
Ala Ala Glu Ala Ser Arg Leu Thr Phe Pro Thr Asn Pro Ser Arg Arg
35 40 45

ctc gct agc cga aac ctg ccc agc cgg tgc ccg gcc act gcg cac gcg 191
Leu Ala Ser Arg Asn Leu Pro Ser Arg Cys Pro Ala Thr Ala His Ala
50 55 60

cgg gac gac gtc acg tgc gct ccc ggg gct gga cgg agc tgg cag gag 239
Arg Asp Asp Val Thr Cys Ala Pro Gly Ala Gly Arg Ser Trp Gln Glu
65 70 75

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ctg gca gga ggg gcc ttg cca gct tcc gcc gcc gcg tcg ttt cag gac 287
Leu Ala Gly Gly Ala Leu Pro Ala Ser Ala Ala Ser Phe Gln Asp
80 85 90 95

ccg gac ggc gga ttc gcg ctg cct ccg ccg ccg cgg ggc agc cgg ggg 335
Pro Asp Gly Gly Phe Ala Leu Pro Pro Pro Arg Gly Ser Arg Gly
100 105 110

gca ggg agc cca gcg agg ggc gcg cgt ggg cgc ggc cat ggg act gcg 383
Ala Gly Ser Phe Ala Arg Gly Ala Arg Gly Arg Gly His Gly Thr Ala
115 120 125

ccg gat ccg gtg aca gca ggg agc caa gcg gcc cgg gcc ctg agc gcg 431
Pro Asp Pro Val Thr Ala Gly Ser Gln Ala Ala Arg Ala Leu Ser Ala
130 135 140

tct tct ccg ggg ggc ctc gcc ctc ctg ctc gcg ggg ccg ggg ctc ctg 479
Ser Ser Pro Gly Gly Leu Ala Leu Leu Ala Gly Pro Gly Leu Leu
145 150 155

ctc cgg ttg ctg gcg ctg ttg ctg gct gtg gcg gcg gcc agg atc atg 527
Leu Arg Leu Leu Ala Leu Leu Leu Ala Val Ala Ala Ala Arg Ile Met
160 165 170 175

tcg ggt cgc cgc tgc gcc ggc ggg gga gcg gcc tgc gcg agc gcc gcg 575
Ser Gly Arg Arg Cys Ala Gly Gly Gly Ala Ala Cys Ala Ser Ala Ala
180 185 190

gcc gag gcc gtg gag ccg gcc gcc cga gag ctg ttc gag gcg tgc 620
Ala Glu Ala Val Glu Pro Ala Ala Arg Glu Leu Phe Glu Ala Cys
195 200 205

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<210> 114

<211> 206

<212> PRT

<213> Homo sapiens

<400> 114

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Lys Thr Thr Thr Thr Lys Asn Thr Ile Cys Arg Ile Val Arg Leu Gln
1 5 10 15

Gln Asn Pro Pro Gln Arg Trp Arg Trp Asp Glu Ala Pro Ser Pro Ala
20 25 30

Ala Glu Ala Ser Arg Leu Thr Phe Pro Thr Asn Pro Ser Arg Arg Leu
35 40 45

Ala Ser Arg Asn Leu Pro Ser Arg Cys Pro Ala Thr Ala His Ala Arg
50 55 60

Asp Asp Val Thr Cys Ala Pro Gly Ala Gly Arg Ser Trp Gln Glu Leu
65 70 75 80

Ala Gly Gly Ala Leu Pro Ala Ser Ala Ala Ser Phe Gln Asp Pro
85 90 95

Asp Gly Gly Phe Ala Leu Pro Pro Pro Pro Arg Gly Ser Arg Gly Ala
100 105 110

Gly Ser Pro Ala Arg Gly Ala Arg Gly Arg Gly His Gly Thr Ala Pro
115 120 125

Asp Pro Val Thr Ala Gly Ser Gln Ala Ala Arg Ala Leu Ser Ala Ser
130 135 140

Ser Pro Gly Gly Leu Ala Leu Leu Leu Ala Gly Pro Gly Leu Leu Leu
145 150 155 160

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Arg	Leu	Leu	Ala	Leu	Leu	Leu	Ala	Val	Ala	Ala	Ala	Arg	Ile	Met	Ser
			165						170					175	
Gly	Arg	Arg	Cys	Ala	Gly	Gly	Gly	Ala	Ala	Cys	Ala	Ser	Ala	Ala	Ala
			180					185					190		
Glu	Ala	Val	Glu	Pro	Ala	Ala	Arg	Glu	Leu	Phe	Glu	Ala	Cys		
		195					200					205			

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<210> 115
<211> 1039
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (287)..(1039)
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<400> 115
gtacaatatt gatttcaaaa aagttcctct aatcaatcct gagctaataa cttactgtgg 60
aaagagtaat tgatcagagc catccctcca attggagtca actttcatga ctgttcggat 120
ttccttttatt ttgggggcag ttcatecaaa cttctattaa acggcaacta gttcactttt 180
gagaagtggt ttacaagaaa caacaacaac aacaacaaag cagttgcgga ggaaagaaaa 240
gagacaaagt aaaaaaacg gaaaaaagaat ctcccaggag aaaggg atg tgg aag      295
                                     Met Trp Lys
                                     1

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ctg aaa aca cgg aca att tcc aca gta aga ctt cca aaa gaa tgt gca 343
Leu Lys Thr Arg Thr Ile Ser Thr Val Arg Leu Pro Lys Glu Cys Ala
5 10 15

aga tcc gag caa aac ttt caa ggg ctc ttt ttc agt gta atg gta gtg 391
Arg Ser Glu Gln Asn Phe Gln Gly Leu Phe Phe Ser Val Met Val Val
20 25 30 35

aga aag ttc agc ctg gaa agc cca ggg ctt aaa aca aca aca aca aaa 439
Arg Lys Phe Ser Leu Glu Ser Pro Gly Leu Lys Thr Thr Thr Thr Lys
40 45 50

aac aca ata tgc agg atc gtt cgg ctt cag cag aac cca ccg caa aga 487
Asn Thr Ile Cys Arg Ile Val Arg Leu Gln Gln Asn Pro Pro Gln Arg
55 60 65

tgg cgg tgg gac gaa gcc cct tct ccc gcc gcc gaa gcc tct cgc ctc 535
Trp Arg Trp Asp Glu Ala Pro Ser Pro Ala Ala Glu Ala Ser Arg Leu
70 75 80

aca ttt ccc aca aac cct tgg cgc cgc ctc gct agc cga aac ctg ccc 583
Thr Phe Pro Thr Asn Pro Ser Arg Arg Leu Ala Ser Arg Asn Leu Pro
85 90 95

agc cgg tgc ccg gcc act gcg cac gcg cgg gac gac gtc acg tgc gct 631
 Ser Arg Cys Pro Ala Thr Ala His Ala Arg Asp Asp Val Thr Cys Ala
 100 105 110 115

ccc ggg gct gga cgg agc tgg cag gag ctg gca gga ggg gcc ttg cca 679
Pro Gly Ala Gly Arg Ser Trp Gln Glu Leu Ala Gly Gly Ala Leu Pro
120 125 130

gct tcc gcc gcc gcg tcg ttt cag gac ccg gac ggc gga ttc gcg ctg 727
Ala Ser Ala Ala Ala Ser Phe Gln Asp Pro Asp Gly Gly Phe Ala Leu
135 140 145

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cct ccg ccg ccg cgg ggc agc cgg ggg gca ggg agc cca gcg agg ggc 775
 Pro Pro Pro Pro Arg Gly Ser Arg Gly Ala Gly Ser Pro Ala Arg Gly
 150 155 160

gcg cgt ggg cgc ggc cat ggg act gcg ccg gat ccg gtg aca gca ggg 823
 Ala Arg Gly Arg Gly His Gly Thr Ala Pro Asp Pro Val Thr Ala Gly
 165 170 175

agc caa gcg gcc cgg gcc ctg agc gcg tct tct ccg ggg ggc ctc gcc 871
 Ser Gln Ala Ala Arg Ala Leu Ser Ala Ser Ser Pro Gly Gly Leu Ala
 180 185 190 195

ctc ctg ctc gcg ggg ccg ggg ctc ctg ctc ccg ttg ctg gcg ctg ttg 919
 Leu Leu Leu Ala Pro Gly Leu Leu Arg Leu Leu Ala Leu Leu
 200 205 210

ctg gct gtg gcg gcg gcc agg atc atg tcg ggt cgc cgc tgc gcc ggc 967
 Leu Ala Val Ala Ala Ala Arg Ile Met Ser Gly Arg Arg Cys Ala Gly
 215 220 225

ggg gga gcg gcc tgc gcg agc gcc gcg gcc gag gcc gtg gag ccg gcc 1015
 Gly Gly Ala Ala Cys Ala Ser Ala Ala Ala Glu Ala Val Glu Pro Ala
 230 235 240

gcc cga gag ctg ttc gag gcg tgc 1039
 Ala Arg Glu Leu Phe Glu Ala Cys
 245 250

<210> 116
 <211> 251
 <212> PRT
 <213> Homo sapiens

<400> 116
 Met Trp Lys Leu Lys Thr Arg Thr Ile Ser Thr Val Arg Leu Pro Lys
 1 5 10 15

Glu Cys Ala Arg Ser Glu Gln Asn Phe Gln Gly Leu Phe Phe Ser Val
 20 25 30

Met Val Val Arg Lys Phe Ser Leu Glu Ser Pro Gly Leu Lys Thr Thr
 35 40 45

Thr Thr Lys Asn Thr Ile Cys Arg Ile Val Arg Leu Gln Gln Asn Pro
 50 55 60

Pro Gln Arg Trp Arg Trp Asp Glu Ala Pro Ser Pro Ala Ala Glu Ala
 65 70 75 80

Ser Arg Leu Thr Phe Pro Thr Asn Pro Ser Arg Arg Leu Ala Ser Arg
 85 90 95

Asn Leu Pro Ser Arg Cys Pro Ala Thr Ala His Ala Arg Asp Asp Val
 100 105 110

Thr Cys Ala Pro Gly Ala Gly Arg Ser Trp Gln Glu Leu Ala Gly Gly
 115 120 125

Ala Leu Pro Ala Ser Ala Ala Ala Ser Phe Gln Asp Pro Asp Gly Gly
 130 135 140

Phe Ala Leu Pro Pro Pro Arg Gly Ser Arg Gly Ala Gly Ser Pro
 145 150 155 160

Ala Arg Gly Ala Arg Gly Arg Gly His Gly Thr Ala Pro Asp Pro Val
 165 170 175

Thr Ala Gly Ser Gln Ala Ala Arg Ala Leu Ser Ala Ser Ser Pro Gly
 180 185 190

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Gly Leu Ala Leu Leu Leu Ala Gly Pro Gly Leu Leu Leu Arg Leu Leu
 195 200 205

Ala Leu Leu Leu Ala Val Ala Ala Ala Arg Ile Met Ser Gly Arg Arg
 210 215 220

Cys Ala Gly Gly Gly Ala Ala Cys Ala Ser Ala Ala Ala Glu Ala Val
 225 230 235 240

Glu Pro Ala Ala Arg Glu Leu Phe Glu Ala Cys
 245 250

<210> 117
 <211> 473
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (3)..(473)

<400> 117
 ct agc cga aac ctg ccc agc cgg tgc ccg gcc act gcg cac gcg cgg 47
 Ser Arg Asn Leu Pro Ser Arg Cys Pro Ala Thr Ala His Ala Arg
 1 5 10 15

gac gac gtc acg tgc gct ccc ggg gct gga cgg agc tgg cag gag ctg 95
 Asp Asp Val Thr Cys Ala Pro Gly Ala Gly Arg Ser Trp Gln Glu Leu
 20 25 30

gca gga ggg gcc ttg cca gct tcc gcc gcc gcg tcg ttt cag gac ccg 143
 Ala Gly Gly Ala Leu Pro Ala Ser Ala Ala Ala Ser Phe Gln Asp Pro
 35 40 45

gac ggc gga ttc gcg ctg cct ccg ccg ccg cgg ggc agc cgg ggg gca 191
 Asp Gly Gly Phe Ala Leu Pro Pro Pro Arg Gly Ser Arg Gly Ala
 50 55 60

ggg agc cca gcg agg ggc gcg cgt ggg cgc ggc cat ggg act gcg ccg 239
 Gly Ser Pro Ala Arg Gly Ala Arg Gly Arg Gly His Gly Thr Ala Pro
 65 70 75

gat ccg gtg aca gca ggg agc caa gcg gcc cgg gcc ctg agc gcg tct 287
 Asp Pro Val Thr Ala Gly Ser Gln Ala Ala Arg Ala Leu Ser Ala Ser
 80 85 90 95

tct ccg ggg ggc ctc gcc ctc ctg ctc gcg ggg ccg ggg ctc ctg ctc 335
 Ser Pro Gly Gly Leu Ala Leu Leu Leu Ala Gly Pro Gly Leu Leu Leu
 100 105 110

cgg ttg ctg gcg ctg ttg ctg gct gtg gcg gcg gcc agg atc atg tcg 383
 Arg Leu Leu Ala Leu Leu Leu Ala Val Ala Ala Ala Arg Ile Met Ser
 115 120 125

ggt cgc cgc tgc gcc ggc ggg gga gcg gcc tgc gcg agc gcc gcg gcc 431
 Gly Arg Arg Cys Ala Gly Gly Gly Ala Ala Cys Ala Ser Ala Ala Ala
 130 135 140

gag gcc gtg gag ccg gcc gcc cga gag ctg ttc gag gcg tgc 473
 Glu Ala Val Glu Pro Ala Ala Arg Glu Leu Phe Glu Ala Cys
 145 150 155

<210> 118
 <211> 157
 <212> PRT
 <213> Homo sapiens

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<400> 118

Ser Arg Asn Leu Pro Ser Arg Cys Pro Ala Thr Ala His Ala Arg Asp
 1 5 10 15

Asp Val Thr Cys Ala Pro Gly Ala Gly Arg Ser Trp Gln Glu Leu Ala
 20 25 30

Gly Gly Ala Leu Pro Ala Ser Ala Ala Ala Ser Phe Gln Asp Pro Asp
 35 40 45

Gly Gly Phe Ala Leu Pro Pro Pro Pro Arg Gly Ser Arg Gly Ala Gly
 50 55 60

Ser Pro Ala Arg Gly Ala Arg Gly Arg Gly His Gly Thr Ala Pro Asp
 65 70 75 80

Pro Val Thr Ala Gly Ser Gln Ala Ala Arg Ala Leu Ser Ala Ser Ser
 85 90 95

Pro Gly Gly Leu Ala Leu Leu Leu Ala Gly Pro Gly Leu Leu Leu Arg
 100 105 110

Leu Leu Ala Leu Leu Leu Ala Val Ala Ala Ala Arg Ile Met Ser Gly
 115 120 125

Arg Arg Cys Ala Gly Gly Gly Ala Ala Cys Ala Ser Ala Ala Ala Glu
 130 135 140

Ala Val Glu Pro Ala Ala Arg Glu Leu Phe Glu Ala Cys
 145 150 155

<210> 119

<211> 22

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Primer

<400> 119

gttcctctaa tcaatcctga gc

22

<210> 120

<211> 26

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Primer

<400> 120

ggaaagagta attgacaga gccatc

26

<210> 121

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Primer

<400> 121

cgccgaagcc tctcgctca catttcc

27

<210> 122

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<211> 27
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:Primer

<400> 122
 ggaaatgtga ggcgagaggc ttcggcg

27

<210> 123
 <211> 659
 <212> DNA
 <213> Homo sapiens

<400> 123
 ggaaagagta attgatcaga gccatccctc caattggagt caacttccat gactgttcgg 60
 atttccttta ttttgggggc agttcatcca aacttctatt aaacggcaac tagttcactt 120
 ttgagaagtg gtttacaaga aacaacaaca acaacaacaa agcagttgcg gaggaagaa 180
 aagagacaaa gtaaaaaaaa cggaaaagaa atctcccagg agaaagggat gtggaagctg 240
 aaaacacgga caatttccac agtaagactt ccaaaagaat gtgcaagatc cgagcaaaac 300
 tttcaagggc tctttttcag tgtaatggta gtgagaaagt tcagcctgga aagcccaggg 360
 cttaaaacaa caacaacaaa aaacacaata tgcaggatcg ttcggcttca gcagaaccca 420
 ccgcaaaagt ggcggtggga cgaagccctc tctcccgccg ccgaagcctc tcgcctcaca 480
 tttccacaaa acccttcgcg ccgcctcgct agccgaaacc tgcccagccg gtgcccggcc 540
 actgcgcacg cgcgggacga cgtcacgtgc gctcccgggg ctggacggag ctggcaggag 600
 gggccttgcc agcttccgcc gccgcgtcgt ttcaggaccc ggacggcgga ttcgcgctg 659

<210> 124
 <211> 669
 <212> DNA
 <213> Homo sapiens

<400> 124
 ggaaagagta attgatcaga gccatccctc caattggagt caacttccat gactgttcgg 60
 atttccttta ttttgggggc agttcatcca aacttctatt aaacggcaac tagttcactt 120
 ttgagaagtg gtttacaaga aacaacaaca acaacaacaa agcagttgcg gaggaagaa 180
 aagagacaaa gtaaaaaaaa cggaaaagaa atctcccagg agaaagggat gtggaagctg 240
 aaaacacgga caatttccac agtaagactt ccaaaagaat gtgcaagatc cgagcaaaac 300
 tttcaagggc tctttttcag tgtaatggta gtgagaaagt tcagcctgga aagcccaggg 360
 cttaaaacaa caacaacaaa aaacacaata tgcaggatcg ttcggcttca gcagaaccca 420
 ccgcaaaagt ggcggtggga cgaagccctc tctcccgccg ccgaagcctc tcgcctcaca 480
 tttccacaaa acccttcgcg ccgcctcgct agccgaaacc tgcccagccg gtgcccggcc 540
 actgcgcacg cgcgggacga cgtcacgtgc gctcccgggg ctggacggag ctggcaggag 600
 gggccaggag gggccttgcc agcttccgcc gccgcgtcgt ttcaggaccc ggacggcgga 660
 ttcgcgctg 669

<210> 125
 <211> 659
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 ttgagaagtg gtttacaaga aacaacaaca acaacaacaa agcagttgcg gaggaagaa 180
 aagagacaaa gtaaaaaaaa cggaaaagaa atctcccagg agaaagggat gtggaagctg 240
 aaaacacgga caatttccac agtaagactt ccaaaagaat gtgcaagatc cgagcaaaac 300
 tttcaagggc tctttttcag tgtaatggta gtgagaaagt tcagcctgga aagcccaggg 360
 cttaaaacaa caacaacaaa aaacacaata tgcaggatcg ttcggcttca gcagaaccca 420
 ccgcaaaagt ggcggtggga cgaagccctc tctcccgccg ccgaagcctc tcgcctcaca 480
 tttccacaaa acccttcgcg ccgcctcgct agccgaaacc tgcccagccg gtgcccggcc 540
 actgcgcacg cgcgggacga cgtcacgtgc gctcccgggg ctggacggag ctggcaggag 600
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<210> 126

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<211> 659
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ttgagaagtg gtttacaaga aacaacaaca acaacaacaa agcagttgcy gaggaagaa 180
aagagacaaa gtaaaaaaaa cggaaaagaa atctcccagg agaaagggat gtggaagctg 240
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ccgcaaagat ggcggtggga cgaagccctt tctcccgcg ccgaagcctc tcgcctcaca 480
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actgcgcacg cgcgggacga cgtcacgtgc gctcccgggg ctggacggag ctggcaggag 600
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ttgagaagtg gtttacaaga aacaacaaca acaacaacaa agcagttgcy gaggaagaa 180
aagagacaaa gtaaaaaaaa cggaaaagaa atctcccagg agaaagggat gtggaagctg 240
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cttaaaacaa caacaacaaa aaacacaata tgcaggatcg ttcggcttca gcagaaccca 420
ccgcaaagat ggcggtggga cgaagccctt tctcccgcg ccgaagcctc tcgcctcaca 480
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actgcgcacg cgcgggacga cgtcacgtgc gctcccgggg ctggacggag ctggcaggag 600
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ttgagaagtg gtttacaaga aacaacaaca acaacaacaa agcagttgcy gaggaagaa 180
aagagacaaa gtaaaaaaaa cggaaaagaa atctcccagg agaaagggat gtggaagctg 240
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ccgcaaagat ggcggtggga cgaagccctt tctcccgcg ccgaagcctc tcgcctcaca 480
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actgcgcacg cgcgggacga cgtcacgtgc gctcccgggg ctggacggag ctggcaggag 600
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ttcgcgctg 669

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ttgagaagtg gtttacaaga aacaacaaca acaacaacaa agcagttgcy gaggaagaa 180
aagagacaaa gtaaaaaaaa cggaaaagaa atctcccagg agaaagggat gtggaagctg 240
aaaacacgga caatttccac agtaagactt ccaaaaagaat gtgcaagatc cgagcaaaac 300
tttcaagggc tctttttcag tgtaatggta gtgagaaagt tcagcctgga aagcccaggg 360
cttaaaacaa caacaacaaa aaacacaata tgcaggatcg ttcggcttca gcagaaccca 420

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ccgcaaagat ggcggtggga cgaagccct tctcccgccg ccgaagcctc tcgcctcaca 480
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<400> 130
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<210> 131
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 aagagacaaa gtaaaaaaaaa cggaaaagaa atctcccagg agaaaggg atg tgg aag 237
 Met Trp Lys
 1

ctg aaa aca cgg aca att tcc aca gta aga ctt cca aaa gaa tgt gca 285
 Leu Lys Thr Arg Thr Ile Ser Thr Val Arg Leu Pro Lys Glu Cys Ala
 5 10 15

aga tcc gag caa aac ttt caa ggg ctc ttt ttc agt gta atg gta gtg 333
 Arg Ser Glu Gln Asn Phe Gln Gly Leu Phe Phe Ser Val Met Val Val
 20 25 30 35

aga aag ttc agc ctg gaa agc cca ggg ctt aaa aca aca aca aca aaa 381
 Arg Lys Phe Ser Leu Glu Ser Pro Gly Leu Lys Thr Thr Thr Thr Lys
 40 45 50

aac aca ata tgc agg atc gtt cgg ctt cag cag aac cca ccg caa aga 429
 Asn Thr Ile Cys Arg Ile Val Arg Leu Gln Gln Asn Pro Pro Gln Arg
 55 60 65

tgg cgg tgg gac gaa gcc cct tct ccc gcc gcc gaa gcc tct cgc ctc 477
 Trp Arg Trp Asp Glu Ala Pro Ser Pro Ala Ala Glu Ala Ser Arg Leu
 70 75 80

aca ttt ccc aca aac cct tcg cgc cgc ctc gct agc cga aac ctg ccc 525
 Thr Phe Pro Thr Asn Pro Ser Arg Arg Leu Ala Ser Arg Asn Leu Pro
 85 90 95

agc cgg tgc ccg gcc act gcg cac gcg cgg gac gac gtc acg tgc gct 573
 Ser Arg Cys Pro Ala Thr Ala His Ala Arg Asp Asp Val Thr Cys Ala
 100 105 110 115

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Pro Gly Ala Gly Arg Ser Trp Gln Glu Leu Ala Gly Gly Ala Leu Pro	
120 125 130	
gct tcc gcc gcc cgg tcc ttt cag gac ccg gac ggc gga ttc gcg ctg	669
Ala Ser Ala Ala Ala Ser Phe Gln Asp Pro Asp Gly Gly Phe Ala Leu	
135 140 145	
cct ccg ccg ccg cgg ggc agc cgg ggg gca ggg agc cca gcg agg ggc	717
Pro Pro Pro Pro Arg Gly Ser Arg Gly Ala Gly Ser Pro Ala Arg Gly	
150 155 160	
gcg cgt ggg cgc ggc cat ggg act gcg ccg gat ccg gtg aca gca ggg	765
Ala Arg Gly Arg Gly His Gly Thr Ala Pro Asp Pro Val Thr Ala Gly	
165 170 175	
agc caa gcg gcc cgg gcc ctg agc gcg tct tct ccg ggg ggc ctc gcc	813
Ser Gln Ala Ala Arg Ala Leu Ser Ala Ser Pro Gly Gly Leu Ala	
180 185 190 195	
ctc ctg ctc gcg ggg ccg ggg ctc ctg ctc ccg ttg ctg gcg ctg ttg	861
Leu Leu Leu Ala Gly Pro Gly Leu Leu Leu Arg Leu Leu Ala Leu Leu	
200 205 210	
ctg gct gtg gcg gcg gcc agg atc atg tcc ggt cgc cgc tgc gcc ggc	909
Leu Ala Val Ala Ala Ala Arg Ile Met Ser Gly Arg Arg Cys Ala Gly	
215 220 225	
ggg gga gcg gcc tgc gcg agc gcc gcg gcc gag gcc gtg gag ccg gcc	957
Gly Gly Ala Ala Cys Ala Ser Ala Ala Ala Glu Ala Val Glu Pro Ala	
230 235 240	
gcc cga gag ctg ttc gag gcg tgc cgc aac ggg gac gtg gaa cga gtc	1005
Ala Arg Glu Leu Phe Glu Ala Cys Arg Asn Gly Asp Val Glu Arg Val	
245 250 255	
aag agg ctg gtg acg cct gag aag gtg aac agc cgc gac acg gcg ggc	1053
Lys Arg Leu Val Thr Pro Glu Lys Val Asn Ser Arg Asp Thr Ala Gly	
260 265 270 275	
agg aaa tcc acc ccg ctg cac ttc gcc gca ggt ttt ggg cgg aaa gac	1101
Arg Lys Ser Thr Pro Leu His Phe Ala Ala Gly Phe Gly Arg Lys Asp	
280 285 290	
gta gtt gaa tat ttg ctt cag aat ggt gca aat gtc caa gca cgt gat	1149
Val Val Glu Tyr Leu Leu Gln Asn Gly Ala Asn Val Gln Ala Arg Asp	
295 300 305	
gat ggg ggc ctt att cct ctt cat aat gca tgc tct ttt ggt cat gct	1197
Asp Gly Gly Leu Ile Pro Leu His Asn Ala Cys Ser Phe Gly His Ala	
310 315 320	
gaa gta gtc aat ctc ctt ttg cga cat ggt gca gac ccc aat gct cga	1245
Glu Val Val Asn Leu Leu Leu Arg His Gly Ala Asp Pro Asn Ala Arg	
325 330 335	
gat aat tgg aat tat act cct ctc cat gaa gct gca att aaa gga aag	1293
Asp Asn Trp Asn Tyr Thr Pro Leu His Glu Ala Ala Ile Lys Gly Lys	
340 345 350 355	
att gat gtt tgc att gtg ctg tta cag cat gga gct gag cca acc atc	1341
Ile Asp Val Cys Ile Val Leu Leu Gln His Gly Ala Glu Pro Thr Ile	
360 365 370	
cga aat aca gat gga agg aca gca ttg gat tta gca gat cca tct gcc	1389
Arg Asn Thr Asp Gly Arg Thr Ala Leu Asp Leu Ala Asp Pro Ser Ala	
375 380 385	

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aaa gca gtg ctt act ggt gaa tat aag aaa gat gaa ctc tta gaa agt	1437
Lys Ala Val Leu Thr Gly Glu Tyr Lys Lys Asp Glu Leu Leu Glu Ser	
390 395 400	
gcc agg agt ggc aat gaa gaa aaa atg atg gct cta ctc aca cca tta	1485
Ala Arg Ser Gly Asn Glu Glu Lys Met Met Ala Leu Leu Thr Pro Leu	
405 410 415	
aat gtc aac tgc cac gca agt gat ggc aga aag tca act cca tta cat	1533
Asn Val Asn Cys His Ala Ser Asp Gly Arg Lys Ser Thr Pro Leu His	
420 425 430 435	
ttg gca gca gga tat aac aga gta aag att gta cag ctg tta ctg caa	1581
Leu Ala Ala Gly Tyr Asn Arg Val Lys Ile Val Gln Leu Leu Leu Gln	
440 445 450	
cat gga gct gat gtc cat gct aaa gat aaa ggt gat ctg gta cca tta	1629
His Gly Ala Asp Val His Ala Lys Asp Lys Gly Asp Leu Val Pro Leu	
455 460 465	
cac aat gcc tgt tct tat ggt cat tat gaa gta act gaa ctt ttg gtc	1677
His Asn Ala Cys Ser Tyr Gly His Tyr Glu Val Thr Glu Leu Leu Val	
470 475 480	
aag cat ggt gcc tgt gta aat gca atg gac ttg tgg caa ttc act cct	1725
Lys His Gly Ala Cys Val Asn Ala Met Asp Leu Trp Gln Phe Thr Pro	
485 490 495	
ctt cat gag gca gct tct aag aac agg gtt gaa gta tgt tct ctt ctc	1773
Leu His Glu Ala Ala Ser Lys Asn Arg Val Glu Val Cys Ser Leu Leu	
500 505 510 515	
tta agt tat ggt gca gac cca aca ctg ctc aat tgt cac aat aaa agt	1821
Leu Ser Tyr Gly Ala Asp Pro Thr Leu Leu Asn Cys His Asn Lys Ser	
520 525 530	
gct ata gac ttg gct ccc aca cca cag tta aaa gaa aga tta gca tat	1869
Ala Ile Asp Leu Ala Pro Thr Pro Gln Leu Lys Glu Arg Leu Ala Tyr	
535 540 545	
gaa ttt aaa ggc cac tcg ttg ctg caa gct gca cga gaa gct gat gtt	1917
Glu Phe Lys Gly His Ser Leu Leu Gln Ala Ala Arg Glu Ala Asp Val	
550 555 560	
act cga atc aaa aaa cat ctc tct ctg gaa atg gtg aat ttc aag cat	1965
Thr Arg Ile Lys Lys His Leu Ser Leu Glu Met Val Asn Phe Lys His	
565 570 575	
cct caa aca cat gaa aca gca ttg cat tgt gct gct gca tct cca tat	2013
Pro Gln Thr His Glu Thr Ala Leu His Cys Ala Ala Ser Pro Tyr	
580 585 590 595	
ccc aaa aga aag caa ata tgt gaa ctg ttg cta aga aaa gga gca aac	2061
Pro Lys Arg Lys Gln Ile Cys Glu Leu Leu Leu Arg Lys Gly Ala Asn	
600 605 610	
atc aat gaa aag act aaa gaa ttc ttg act cct ctg cac gtg gca tct	2109
Ile Asn Glu Lys Thr Lys Glu Phe Leu Thr Pro Leu His Val Ala Ser	
615 620 625	
gag aaa gct cat aat gat gtt gtt gaa gta gtg gtg aaa cat gaa gca	2157
Glu Lys Ala His Asn Asp Val Val Glu Val Val Val Lys His Glu Ala	
630 635 640	
aag gtt aat gct ctg gat aat ctt ggt cag act tct cta cac aga gct	2205
Lys Val Asn Ala Leu Asp Asn Leu Gly Gln Thr Ser Leu His Arg Ala	
645 650 655	

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gca tat tgt ggt cat cta caa acc tgc cgc cta ctc ctg agc tat ggg	2253
Ala Tyr Cys Gly His Leu Gln Thr Cys Arg Leu Leu Leu Ser Tyr Gly	
660 665 670 675	
tgt gat cct aac att ata tcc ctt cag ggc ttt act gct tta cag atg	2301
Cys Asp Pro Asn Ile Ile Ser Leu Gln Gly Phe Thr Ala Leu Gln Met	
680 685 690	
gga aat gaa aat gta cag caa ctc ctc caa gag ggt atc tca tta ggt	2349
Gly Asn Glu Ala Val Gln Gln Leu Leu Gln Glu Gly Ile Ser Leu Gly	
695 700 705	
aat tca gag gca gac aga caa ttg ctg gaa gct gca aag gct gga gat	2397
Asn Ser Glu Ala Asp Arg Gln Leu Glu Ala Ala Lys Ala Gly Asp	
710 715 720	
gtc gaa act gta aaa aaa ctg tgt act gtt cag agt gtc aac tgc aga	2445
Val Glu Thr Val Lys Lys Leu Cys Thr Val Gln Ser Val Asn Cys Arg	
725 730 735	
gac att gaa ggg cgt cag tct aca cca ctt cat ttt gca gct ggg tat	2493
Asp Ile Glu Gly Arg Gln Ser Thr Pro Leu His Phe Ala Ala Gly Tyr	
740 745 750 755	
aac aga gtg tcc gtg gtg gaa tat ctg cta cag cat gga gct gat gtg	2541
Asn Arg Val Ser Val Val Glu Tyr Leu Leu Gln His Gly Ala Asp Val	
760 765 770	
cat gct aaa gat aaa gga ggc ctt gta cct ttg cac aat gca tgt tct	2589
His Ala Lys Asp Lys Gly Gly Leu Val Pro Leu His Asn Ala Cys Ser	
775 780 785	
tat gga cat tat gaa gtt gca gaa ctt ctt gtt aaa cat gga gca gta	2637
Tyr Gly His Tyr Glu Val Ala Glu Leu Leu Val Lys His Gly Ala Val	
790 795 800	
gtt aat gta gct gat tta tgg aaa ttt aca cct tta cat gaa gca gca	2685
Val Asn Val Ala Asp Leu Trp Lys Phe Thr Pro Leu His Glu Ala Ala	
805 810 815	
gca aaa gga aaa tat gaa att tgc aaa ctt ctg ctc cag cat ggt gca	2733
Ala Lys Gly Lys Tyr Glu Ile Cys Lys Leu Leu Leu Gln His Gly Ala	
820 825 830 835	
gac cct aca aaa aaa aac agg gat gga aat act cct ttg gat ctt gtt	2781
Asp Pro Thr Lys Lys Asn Arg Asp Gly Asn Thr Pro Leu Asp Leu Val	
840 845 850	
aaa gat gga gat aca gat att caa gat ctg ctt agg gga gat gca gct	2829
Lys Asp Gly Asp Thr Asp Ile Gln Asp Leu Leu Arg Gly Asp Ala Ala	
855 860 865	
ttg cta gat gct gcc aag aag ggt tgt tta gcc aga gtg aag aag ttg	2877
Leu Leu Asp Ala Ala Lys Lys Gly Cys Leu Ala Arg Val Lys Lys Leu	
870 875 880	
tct tct cct gat aat gta aat tgc cgc gat acc caa ggc aga cat tca	2925
Ser Ser Pro Asp Asn Val Asn Cys Arg Asp Thr Gln Gly Arg His Ser	
885 890 895	
aca cct tta cat tta gca gct ggt tat aat aat tta gaa gtt gca gag	2973
Thr Pro Leu His Leu Ala Ala Gly Tyr Asn Asn Leu Glu Val Ala Glu	
900 905 910 915	
tat ttg tta caa cac gga gct gat gtg aat gcc caa gac aaa gga gga	3021
Tyr Leu Leu Gln His Gly Ala Asp Val Asn Ala Gln Asp Lys Gly Gly	
920 925 930	

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ctt att cct tta cat aat gca gca tct tac ggg cat gta gat gta gca	3069
Leu Ile Pro Leu His Asn Ala Ala Ser Tyr Gly His Val Asp Val Ala	
935 940 945	
gct cta cta ata aag tat aat gca tgt gtc aat gcc acg gac aaa tgg	3117
Ala Leu Leu Ile Lys Tyr Asn Ala Cys Val Asn Ala Thr Asp Lys Trp	
950 955 960	
gct ttc aca cct ttg cac gaa gca gcc caa aag gga cga aca cag ctt	3165
Ala Phe Thr Pro Leu His Glu Ala Ala Gln Lys Gly Arg Thr Gln Leu	
965 970 975	
tgt gct ttg ttg cta gcc cat gga gct gac ccg act ctt aaa aat cag	3213
Cys Ala Leu Leu Leu His Glu Ala Asp Pro Thr Leu Lys Asn Gln	
980 985 990 995	
gaa gga caa aca cct tta gat tta gtt tca gca gat gat gtc agc gct	3261
Glu Gly Gln Thr Pro Leu Asp Leu Val Ser Ala Asp Asp Val Ser Ala	
1000 1005 1010	
ctt ctg aca gca gcc atg ccc cca tct gct ctg ccc tct tgt tac aag	3309
Leu Leu Thr Ala Ala Met Pro Pro Ser Ala Leu Pro Ser Cys Tyr Lys	
1015 1020 1025	
cct caa gtg ctg aat ggt gtg aga agc cca gga gcc act gca gat gct	3357
Pro Gln Val Leu Asn Gly Val Arg Ser Pro Gly Ala Thr Ala Asp Ala	
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ctc tct tca ggt cca tct agc cca tca agc ctt tct gca gcc agc agt	3405
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ctt gac aac tta tct ggg agt ttt tca gaa ctg tct tca gta gtt agt	3453
Leu Asp Asn Leu Ser Gly Ser Phe Ser Glu Leu Ser Ser Val Val Ser	
1060 1065 1070 1075	
tca agt gga aca gag ggt gct tcc agt ttg gag aaa aag gag gtt cca	3501
Ser Ser Gly Thr Glu Gly Ala Ser Ser Leu Glu Lys Lys Glu Val Pro	
1080 1085 1090	
gga gta gat ttt agc ata act caa ttc gta agg aat ctt gga ctt gag	3549
Gly Val Asp Phe Ser Ile Thr Gln Phe Val Arg Asn Leu Gly Leu Glu	
1095 1100 1105	
cac cta atg gat ata ttt gag aga gaa cag atc act ttg gat gta tta	3597
His Leu Met Asp Ile Phe Glu Arg Glu Gln Ile Thr Leu Asp Val Leu	
1110 1115 1120	
gtt gag atg ggg cac aag gag ctg aag gag att gga atc aat gct tat	3645
Val Glu Met Gly His Lys Glu Leu Lys Glu Ile Gly Ile Asn Ala Tyr	
1125 1130 1135	
gga cat agg cac aaa cta att aaa gga gtc gag aga ctt atc tcc gga	3693
Gly His Arg His Lys Leu Ile Lys Gly Val Glu Arg Leu Ile Ser Gly	
1140 1145 1150 1155	
caa caa ggt ctt aac cca tat tta act ttg aac acc tct ggt agt gga	3741
Gln Gln Gly Leu Asn Pro Tyr Leu Thr Leu Asn Thr Ser Gly Ser Gly	
1160 1165 1170	
aca att ctt ata gat ctg tct cct gat gat aaa gag ttt cag tct gtg	3789
Thr Ile Leu Ile Asp Leu Ser Pro Asp Asp Lys Glu Phe Gln Ser Val	
1175 1180 1185	
gag gaa gag atg caa agt aca gtt cga gag cac aga gat gga ggt cat	3837
Glu Glu Glu Met Gln Ser Thr Val Arg Glu His Arg Asp Gly Gly His	
1190 1195 1200	

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 Ala Gly Gly Ile Phe Asn Arg Tyr Asn Ile Leu Lys Ile Gln Lys Val
 1205 1210 1215

tgt aac aag aaa cta tgg gaa aga tac act cac cgg aga aaa gaa gtt 3933
 Cys Asn Lys Lys Leu Trp Glu Arg Tyr Thr His Arg Arg Lys Glu Val
 1220 1225 1230 1235

tct gaa gaa aac cac aac cat gcc aat gaa cga atg cta ttt cat ggg 3981
 Ser Glu Glu Asn Val Asn His Ala Asn Glu Arg Met Leu Phe His Gly
 1240 1245 1250

tct cct ttt gtg aat gca att atc cac aaa ggc ttt gat gaa agg cat 4029
 Ser Pro Phe Val Asn Ala Ile Ile His Lys Gly Phe Asp Glu Arg His
 1255 1260 1265

gcg tac ata ggt ggt atg ttt gga gct ggc att tat ttt gct gaa aac 4077
 Ala Tyr Ile Val Gly Met Phe Gly Ala Gly Ile Tyr Phe Ala Glu Asn
 1270 1275 1280

tct tcc aaa agc aat caa tat gta tat gga att gga gga ggt act ggg 4125
 Ser Ser Lys Ser Asn Gln Tyr Val Tyr Gly Ile Gly Gly Gly Thr Gly
 1285 1290 1295

tgt cca gtt cac aaa gac aga tct tgt tac att tgc cac agg cag ctg 4173
 Cys Pro Val His Lys Asp Arg Ser Cys Tyr Ile Cys His Arg Gln Leu
 1300 1305 1310 1315

ctc ttt tgc cgg gta acc ttg gga aag tct ttc ctg cag ttc agt gca 4221
 Leu Phe Cys Arg Val Thr Leu Gly Lys Ser Phe Leu Gln Phe Ser Ala
 1320 1325 1330

atg aaa atg gca cat tct cct cca ggt cat cac tca gtc act ggt agg 4269
 Met Lys Met Ala His Ser Pro Pro Gly His His Ser Val Thr Gly Arg
 1335 1340 1345

ccc agt gta aat ggc cta gca tta gct gaa tat gtt att tac aga gga 4317
 Pro Ser Val Asn Gly Leu Ala Leu Ala Glu Tyr Val Ile Tyr Arg Gly
 1350 1355 1360

gaa cag gct tat cct gag tat tta att act tac cag att atg agg cct 4365
 Glu Gln Ala Tyr Pro Glu Tyr Leu Ile Thr Tyr Gln Ile Met Arg Pro
 1365 1370 1375

gaa ggt atg gtc gat gga taaatagtta ttttaagaaa ctaattccac 4413
 Glu Gly Met Val Asp Gly
 1380 1385

tgaacctaaa atcatcaaag cagcagtggc ctctacgttt tactcctttg ctgaaaaaaaa 4473

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gacttgataa agctttaata atgtacagtg ttttctaaat atttctgtt ttttcagcac 4593

tttacagat gccattccag gttaaactgg gttgtctgta ctaaattata aacagagtta 4653

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taattttact aatacaatac tgtgttcttt aaaacacagc atttacactg aatacaattt 4773

catttgtaaa actgtaaata agagcttttg tactagccca gtatttattt acattgcttt 4833

gtaatataaa tctgttttag aactgcagcg gtttacaaaa ttttttcata tgtattgttc 4893

atctatactt catcttacat cgtcatgatt gagtgatctt tacatttgat tccagaggct 4953

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 35 40 45
 Thr Thr Lys Asn Thr Ile Cys Arg Ile Val Arg Leu Gln Gln Asn Pro
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 Pro Gln Arg Trp Arg Trp Asp Glu Ala Pro Ser Pro Ala Ala Glu Ala
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 Ser Arg Leu Thr Phe Pro Thr Asn Pro Ser Arg Arg Leu Ala Ser Arg
 85 90 95
 Asn Leu Pro Ser Arg Cys Pro Ala Thr Ala His Ala Arg Asp Asp Val
 100 105 110
 Thr Cys Ala Pro Gly Ala Gly Arg Ser Trp Gln Glu Leu Ala Gly Gly
 115 120 125
 Ala Leu Pro Ala Ser Ala Ala Ala Ser Phe Gln Asp Pro Asp Gly Gly
 130 135 140
 Phe Ala Leu Pro Pro Pro Pro Arg Gly Ser Arg Gly Ala Gly Ser Pro
 145 150 155 160
 Ala Arg Gly Ala Arg Gly Arg Gly His Gly Thr Ala Pro Asp Pro Val
 165 170 175
 Thr Ala Gly Ser Gln Ala Ala Arg Ala Leu Ser Ala Ser Ser Pro Gly
 180 185 190
 Gly Leu Ala Leu Leu Leu Ala Gly Pro Gly Leu Leu Leu Arg Leu Leu
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 Ala Leu Leu Leu Ala Val Ala Ala Ala Arg Ile Met Ser Gly Arg Arg
 210 215 220
 Cys Ala Gly Gly Gly Ala Ala Cys Ala Ser Ala Ala Ala Glu Ala Val
 225 230 235 240
 Glu Pro Ala Ala Arg Glu Leu Phe Glu Ala Cys Arg Asn Gly Asp Val
 245 250 255
 Glu Arg Val Lys Arg Leu Val Thr Pro Glu Lys Val Asn Ser Arg Asp
 260 265 270
 Thr Ala Gly Arg Lys Ser Thr Pro Leu His Phe Ala Ala Gly Phe Gly
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 Arg Lys Asp Val Val Glu Tyr Leu Leu Gln Asn Gly Ala Asn Val Gln
 290 295 300
 Ala Arg Asp Asp Gly Gly Leu Ile Pro Leu His Asn Ala Cys Ser Phe
 305 310 315 320
 Gly His Ala Glu Val Val Asn Leu Leu Leu Arg His Gly Ala Asp Pro
 325 330 335

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Asn Ala Arg Asp Asn Trp Asn Tyr Thr Pro Leu His Glu Ala Ala Ile
 340 345 350
 Lys Gly Lys Ile Asp Val Cys Ile Val Leu Leu Gln His Gly Ala Glu
 355 360 365
 Pro Thr Ile Arg Asn Thr Asp Gly Arg Thr Ala Leu Asp Leu Ala Asp
 370 375 380
 Pro Ser Ala Lys Ala Val Leu Thr Gly Glu Tyr Lys Lys Asp Glu Leu
 385 390 395 400
 Leu Glu Ser Ala Arg Ser Gly Asn Glu Glu Lys Met Met Ala Leu Leu
 405 410 415
 Thr Pro Leu Asn Val Asn Cys His Ala Ser Asp Gly Arg Lys Ser Thr
 420 425 430
 Pro Leu His Leu Ala Ala Gly Tyr Asn Arg Val Lys Ile Val Gln Leu
 435 440 445
 Leu Leu Gln His Gly Ala Asp Val His Ala Lys Asp Lys Gly Asp Leu
 450 455 460
 Val Pro Leu His Asn Ala Cys Ser Tyr Gly His Tyr Glu Val Thr Glu
 465 470 475 480
 Leu Leu Val Lys His Gly Ala Cys Val Asn Ala Met Asp Leu Trp Gln
 485 490 495
 Phe Thr Pro Leu His Glu Ala Ala Ser Lys Asn Arg Val Glu Val Cys
 500 505 510
 Ser Leu Leu Leu Ser Tyr Gly Ala Asp Pro Thr Leu Leu Asn Cys His
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 Asn Lys Ser Ala Ile Asp Leu Ala Pro Thr Pro Gln Leu Lys Glu Arg
 530 535 540
 Leu Ala Tyr Glu Phe Lys Gly His Ser Leu Leu Gln Ala Ala Arg Glu
 545 550 555 560
 Ala Asp Val Thr Arg Ile Lys Lys His Leu Ser Leu Glu Met Val Asn
 565 570 575
 Phe Lys His Pro Gln Thr His Glu Thr Ala Leu His Cys Ala Ala Ala
 580 585 590
 Ser Pro Tyr Pro Lys Arg Lys Gln Ile Cys Glu Leu Leu Leu Arg Lys
 595 600 605
 Gly Ala Asn Ile Asn Glu Lys Thr Lys Glu Phe Leu Thr Pro Leu His
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 Val Ala Ser Glu Lys Ala His Asn Asp Val Val Glu Val Val Val Lys
 625 630 635 640
 His Glu Ala Lys Val Asn Ala Leu Asp Asn Leu Gly Gln Thr Ser Leu
 645 650 655
 His Arg Ala Ala Tyr Cys Gly His Leu Gln Thr Cys Arg Leu Leu Leu
 660 665 670
 Ser Tyr Gly Cys Asp Pro Asn Ile Ile Ser Leu Gln Gly Phe Thr Ala
 675 680 685
 Leu Gln Met Gly Asn Glu Asn Val Gln Gln Leu Leu Gln Glu Gly Ile
 690 695 700

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Ser Leu Gly Asn Ser Glu Ala Asp Arg Gln Leu Leu Glu Ala Ala Lys
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 Ala Gly Asp Val Glu Thr Val Lys Lys Leu Cys Thr Val Gln Ser Val
 725 730 735
 Asn Cys Arg Asp Ile Glu Gly Arg Gln Ser Thr Pro Leu His Phe Ala
 740 745 750
 Ala Gly Tyr Asn Arg Val Ser Val Val Glu Tyr Leu Leu Gln His Gly
 755 760 765
 Ala Asp Val His Ala Lys Asp Lys Gly Gly Leu Val Pro Leu His Asn
 770 775 780
 Ala Cys Ser Tyr Gly His Tyr Glu Val Ala Glu Leu Leu Val Lys His
 785 790 795 800
 Gly Ala Val Val Asn Val Ala Asp Leu Trp Lys Phe Thr Pro Leu His
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 Glu Ala Ala Ala Lys Gly Lys Tyr Glu Ile Cys Lys Leu Leu Leu Gln
 820 825 830
 His Gly Ala Asp Pro Thr Lys Lys Asn Arg Asp Gly Asn Thr Pro Leu
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 Asp Leu Val Lys Asp Gly Asp Thr Asp Ile Gln Asp Leu Leu Arg Gly
 850 855 860
 Asp Ala Ala Leu Leu Asp Ala Ala Lys Lys Gly Cys Leu Ala Arg Val
 865 870 875 880
 Lys Lys Leu Ser Ser Pro Asp Asn Val Asn Cys Arg Asp Thr Gln Gly
 885 890 895
 Arg His Ser Thr Pro Leu His Leu Ala Ala Gly Tyr Asn Asn Leu Glu
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 Val Ala Glu Tyr Leu Leu Gln His Gly Ala Asp Val Asn Ala Gln Asp
 915 920 925
 Lys Gly Gly Leu Ile Pro Leu His Asn Ala Ala Ser Tyr Gly His Val
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 Asp Val Ala Ala Leu Leu Ile Lys Tyr Asn Ala Cys Val Asn Ala Thr
 945 950 955 960
 Asp Lys Trp Ala Phe Thr Pro Leu His Glu Ala Ala Gln Lys Gly Arg
 965 970 975
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 980 985 990
 Lys Asn Gln Glu Gly Gln Thr Pro Leu Asp Leu Val Ser Ala Asp Asp
 995 1000 1005
 Val Ser Ala Leu Leu Thr Ala Ala Met Pro Pro Ser Ala Leu Pro Ser
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 1025 1030 1035 1040
 Ala Asp Ala Leu Ser Ser Gly Pro Ser Ser Pro Ser Ser Leu Ser Ala
 1045 1050 1055
 Ala Ser Ser Leu Asp Asn Leu Ser Gly Ser Phe Ser Glu Leu Ser Ser
 1060 1065 1070

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Val Val Ser Ser Ser Gly Thr Glu Gly Ala Ser Ser Leu Glu Lys Lys
 1075 1080 1085
 Glu Val Pro Gly Val Asp Phe Ser Ile Thr Gln Phe Val Arg Asn Leu
 1090 1095 1100
 Gly Leu Glu His Leu Met Asp Ile Phe Glu Arg Glu Gln Ile Thr Leu
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 Asp Val Leu Val Glu Met Gly His Lys Glu Leu Lys Glu Ile Gly Ile
 1125 1130 1135
 Asn Ala Tyr Gly His Arg His Lys Leu Ile Lys Gly Val Glu Arg Leu
 1140 1145 1150
 Ile Ser Gly Gln Gln Gly Leu Asn Pro Tyr Leu Thr Leu Asn Thr Ser
 1155 1160 1165
 Gly Ser Gly Thr Ile Leu Ile Asp Leu Ser Pro Asp Asp Lys Glu Phe
 1170 1175 1180
 Gln Ser Val Glu Glu Glu Met Gln Ser Thr Val Arg Glu His Arg Asp
 1185 1190 1195 1200
 Gly Gly His Ala Gly Gly Ile Phe Asn Arg Tyr Asn Ile Leu Lys Ile
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 Gln Lys Val Cys Asn Lys Lys Leu Trp Glu Arg Tyr Thr His Arg Arg
 1220 1225 1230
 Lys Glu Val Ser Glu Glu Asn His Asn His Ala Asn Glu Arg Met Leu
 1235 1240 1245
 Phe His Gly Ser Pro Phe Val Asn Ala Ile Ile His Lys Gly Phe Asp
 1250 1255 1260
 Glu Arg His Ala Tyr Ile Gly Gly Met Phe Gly Ala Gly Ile Tyr Phe
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 Ala Glu Asn Ser Ser Lys Ser Asn Gln Tyr Val Tyr Gly Ile Gly Gly
 1285 1290 1295
 Gly Thr Gly Cys Pro Val His Lys Asp Arg Ser Cys Tyr Ile Cys His
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 Arg Gln Leu Leu Phe Cys Arg Val Thr Leu Gly Lys Ser Phe Leu Gln
 1315 1320 1325
 Phe Ser Ala Met Lys Met Ala His Ser Pro Pro Gly His His Ser Val
 1330 1335 1340
 Thr Gly Arg Pro Ser Val Asn Gly Leu Ala Leu Ala Glu Tyr Val Ile
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tct gcc aaa gca gtg ctt act ggt gaa tat aag aaa gat gaa ctc tta	1421
Ser Ala Lys Ala Val Leu Thr Gly Glu Tyr Lys Lys Asp Glu Leu Leu	
170 175 180	
gaa agt gcc agg agt ggc aat gaa gaa aaa atg atg gct cta ctc aca	1469
Glu Ser Ala Arg Ser Gly Asn Glu Glu Lys Met Met Ala Leu Leu Thr	
185 190 195	
cca tta aat gtc aac tgc cac gca agt gat ggc aga aag tca act cca	1517
Pro Leu Asn Val Asn Cys His Ala Ser Asp Gly Arg Lys Ser Thr Pro	
200 205 210	
tta cat ttg gca gca gga tat aac aga gta aag att gta cag ctg tta	1565
Leu His Leu Ala Ala Gly Tyr Asn Arg Val Lys Ile Val Gln Leu Leu	
215 220 225 230	
ctg caa cat gga gct gat gtc cat gct aaa gat aaa ggt gat ctg gta	1613
Leu Gln His Gly Ala Asp Val His Ala Lys Asp Lys Gly Asp Leu Val	
235 240 245	
cca tta cac aat gcc tgt tct tat ggt cat tat gaa gta act gaa ctt	1661
Pro Leu His Asn Ala Cys Ser Tyr Gly His Tyr Glu Val Thr Glu Leu	
250 255 260	
ttg gtc aag cat ggt gcc tgt gta aat gca atg gac ttg tgg caa ttc	1709
Leu Val Lys His Gly Ala Cys Val Asn Ala Met Asp Leu Trp Gln Phe	
265 270 275	
act cct ctt cat gag gca gct tct aag aac agg gtt gaa gta tgt tct	1757
Thr Pro Leu His Glu Ala Ala Ser Lys Asn Arg Val Glu Val Cys Ser	
280 285 290	
ctt ctc tta agt tat ggt gca gac cca aca ctg ctc aat tgt cac aat	1805
Leu Leu Leu Ser Tyr Gly Ala Asp Pro Thr Leu Leu Asn Cys His Asn	
295 300 305 310	
aaa agt gct ata gac ttg gct ccc aca cca cag tta aaa gaa aga tta	1853
Lys Ser Ala Ile Asp Leu Ala Pro Thr Pro Gln Leu Lys Glu Arg Leu	
315 320 325	
gca tat gaa ttt aaa ggc cac tcg ttg ctg caa gct gca cga gaa gct	1901
Ala Tyr Glu Phe Lys Gly His Ser Leu Leu Gln Ala Ala Arg Glu Ala	
330 335 340	
gat gtt act cga atc aaa aaa cat ctc tct ctg gaa atg gtg aat ttc	1949
Asp Val Thr Arg Ile Lys Lys His Leu Ser Leu Glu Met Val Asn Phe	
345 350 355	
aag cat cct caa aca cat gaa aca gca ttg cat tgt gct gct gca tct	1997
Lys His Pro Gln Thr His Glu Thr Ala Leu His Cys Ala Ala Ala Ser	
360 365 370	
cca tat ccc aaa aga aag caa ata tgt gaa ctg ttg cta aga aaa gga	2045
Pro Tyr Pro Lys Arg Lys Gln Ile Cys Glu Leu Leu Leu Arg Lys Gly	
375 380 385 390	
gca aac atc aat gaa aag act aaa gaa ttc ttg act cct ctg cac gtg	2093
Ala Asn Ile Asn Glu Lys Thr Lys Glu Phe Leu Thr Pro Leu His Val	
395 400 405	
gca tct gag aaa gct cat aat gat gtt gtt gaa gta gtg gtg aaa cat	2141
Ala Ser Glu Lys Ala His Asn Asp Val Val Glu Val Val Val Lys His	
410 415 420	

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Glu Ala Lys Val Asn Ala Leu Asp Asn Leu Gly Gln Thr Ser Leu His	
425 430 435	
aga gct gca tat tgt ggt cat cta caa acc tgc cgc cta ctc ctg agc	2237
Arg Ala Ala Tyr Cys Gly His Leu Gln Thr Cys Arg Leu Leu Leu Ser	
440 445 450	
tat ggg tgt gat cct aac att ata tcc ctt cag ggc ttt act gct tta	2285
Tyr Gly Cys Asp Pro Asn Ile Ile Ser Leu Gln Gly Phe Thr Ala Leu	
455 460 465 470	
cag atg gga aat gaa aat gta cag caa ctc ctc caa gag ggt atc tca	2333
Gln Met Gly Asn Ser Glu Asn Val Gln Gln Leu Gln Glu Gly Ile Ser	
475 480 485	
tta ggt aat tca gag gca gac aga caa ttg ctg gaa gct gca aag gct	2381
Leu Gly Asn Ser Glu Ala Asp Arg Gln Leu Leu Glu Ala Ala Lys Ala	
490 495 500	
gga gat gtc gaa act gta aaa aaa ctg tgt act gtt cag agt gtc aac	2429
Gly Asp Val Glu Thr Val Lys Lys Leu Cys Thr Val Gln Ser Val Asn	
505 510 515	
tgc aga gac att gaa ggg cgt cag tct aca cca ctt cat ttt gca gct	2477
Cys Arg Asp Ile Glu Gly Arg Gln Ser Thr Pro Leu His Phe Ala Ala	
520 525 530	
ggg tat aac aga gtg tcc gtg gtg gaa tat ctg cta cag cat gga gct	2525
Gly Tyr Asn Arg Val Ser Val Val Glu Tyr Leu Leu Gln His Gly Ala	
535 540 545 550	
gat gtg cat gct aaa gat aaa gga ggc ctt gta cct ttg cac aat gca	2573
Asp Val His Ala Lys Asp Lys Gly Gly Leu Val Pro Leu His Asn Ala	
555 560 565	
tgt tct tat gga cat tat gaa gtt gca gaa ctt ctt gtt aaa cat gga	2621
Cys Ser Tyr Gly His Tyr Glu Val Ala Glu Leu Leu Val Lys His Gly	
570 575 580	
gca gta gtt aat gta gct gat tta tgg aaa ttt aca cct tta cat gaa	2669
Ala Val Val Asn Val Ala Asp Leu Trp Lys Phe Thr Pro Leu His Glu	
585 590 595	
gca gca gca aaa gga aaa tat gaa att tgc aaa ctt ctg ctc cag cat	2717
Ala Ala Ala Lys Gly Lys Tyr Glu Ile Cys Lys Leu Leu Gln His	
600 605 610	
ggt gca gac cct aca aaa aaa aac agg gat gga aat act cct ttg gat	2765
Gly Ala Asp Pro Thr Lys Lys Asn Arg Asp Gly Asn Thr Pro Leu Asp	
615 620 625 630	
ctt gtt aaa gat gga gat aca gat att caa gat ctg ctt agg gga gat	2813
Leu Val Lys Asp Gly Asp Thr Asp Ile Gln Asp Leu Leu Arg Gly Asp	
635 640 645	
gca gct ttg cta gat gct gcc aag aag ggt tgt tta gcc aga gtg aag	2861
Ala Ala Leu Leu Asp Ala Ala Lys Lys Gly Cys Leu Ala Arg Val Lys	
650 655 660	
aag ttg tct tct cct gat aat gta aat tgc cgc gat acc caa ggc aga	2909
Lys Leu Ser Ser Pro Asp Asn Val Asn Cys Arg Asp Thr Gln Gly Arg	
665 670 675	
cat tca aca cct tta cat tta gca gct ggt tat aat aat tta gaa gtt	2957
His Ser Thr Pro Leu His Leu Ala Ala Gly Tyr Asn Asn Leu Glu Val	
680 685 690	

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Ala Glu Tyr Leu Leu Gln His Gly Ala Asp Val Asn Ala Gln Asp Lys	
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gga gga ctt att cct tta cat aat gca gca tct tac ggg cat gta gat	3053
Gly Gly Leu Ile Pro Leu His Asn Ala Ala Ser Tyr Gly His Val Asp	
715 720 725	
gta gca gct cta cta ata aag tat aat gca tgt gtc aat gcc acg gac	3101
Val Ala Ala Leu Leu Ile Lys Tyr Asn Ala Cys Val Asn Ala Thr Asp	
730 735 740	
aaa tgg gct ttc aca cct ttg cac gaa gca gcc caa aag gga cga aca	3149
Lys Trp Ala Phe Thr Pro Leu His Glu Ala Ala Gln Lys Gly Arg Thr	
745 750 755	
cag ctt tgt gct ttg ttg cta gcc cat gga gct gac ccg act ctt aaa	3197
Gln Leu Cys Ala Leu Leu Leu Ala His Gly Ala Asp Pro Thr Leu Lys	
760 765 770	
aat cag gaa gga caa aca cct tta gat tta gtt tca gca gat gat gtc	3245
Asn Gln Glu Gly Gln Thr Pro Leu Asp Leu Val Ser Ala Asp Asp Val	
775 780 785 790	
agc gct ctt ctg aca gca gcc atg ccc cca tct gct ctg ccc tct tgt	3293
Ser Ala Leu Leu Thr Ala Ala Met Pro Pro Ser Ala Leu Pro Ser Cys	
795 800 805	
tac aag cct caa gtg ctc aat ggt gtg aga agc cca gga gcc act gca	3341
Tyr Lys Pro Gln Val Leu Asn Gly Val Arg Ser Pro Gly Ala Thr Ala	
810 815 820	
gat gct ctc tct tca ggt cca tct agc cca tca agc ctt tct gca gcc	3389
Asp Ala Leu Ser Ser Gly Pro Ser Ser Pro Ser Ser Leu Ser Ala Ala	
825 830 835	
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Ser Ser Leu Asp Asn Leu Ser Gly Ser Phe Ser Glu Leu Ser Ser Val	
840 845 850	
gtt agt tca agt gga aca gag ggt gct tcc agt ttg gag aaa aag gag	3485
Val Ser Ser Ser Gly Thr Glu Gly Ala Ser Ser Leu Glu Lys Lys Glu	
855 860 865 870	
gtt cca gga gta gat ttt agc ata act caa ttc gta agg aat ctt gga	3533
Val Pro Gly Val Asp Phe Ser Ile Thr Gln Phe Val Arg Asn Leu Gly	
875 880 885	
ctt gag cac cta atg gat ata ttt gag aga gaa cag atc act ttg gat	3581
Leu Glu His Leu Met Asp Ile Phe Glu Arg Glu Gln Ile Thr Leu Asp	
890 895 900	
gta tta gtt gag atg ggg cac aag gag ctg aag gag att gga atc aat	3629
Val Leu Val Glu Met Gly His Lys Glu Leu Lys Glu Ile Gly Ile Asn	
905 910 915	
gct tat gga cat agg cac aaa cta att aaa gga gtc gag aga ctt atc	3677
Ala Tyr Gly His Arg His Lys Leu Ile Lys Gly Val Glu Arg Leu Ile	
920 925 930	
tcc gga caa caa ggt ctt aac cca tat tta act ttg aac acc tct ggt	3725
Ser Gly Gln Gln Gly Leu Asn Pro Tyr Leu Thr Leu Asn Thr Ser Gly	
935 940 945 950	
agt gga aca att ctt ata gat ctg tct cct gat gat aaa gag ttt cag	3773
Ser Gly Thr Ile Leu Ile Asp Leu Ser Pro Asp Asp Lys Glu Phe Gln	
955 960 965	

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tct gtg gag gaa gag atg caa agt aca gtt cga gag cac aga gat gga 3821
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 970 975 980

ggt cat gca ggt gga atc ttc aac aga tac aat att ctc aag att cag 3869
 Gly His Ala Gly Gly Ile Phe Asn Arg Tyr Asn Ile Leu Lys Ile Gln
 985 990 995

aag gtt tgt aac aag aaa cta tgg gaa aga tac act cac cgg aga aaa 3917
 Lys Val Cys Asn Lys Lys Leu Trp Glu Arg Tyr Thr His Arg Arg Lys
 1000 1005 1010

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 Glu Val Ser Glu Glu Asn His Asn His Ala Asn Glu Arg Met Leu Phe
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 His Gly Ser Pro Phe Val Asn Ala Ile Ile His Lys Gly Phe Asp Glu
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agg cat gcg tac ata ggt ggt atg ttt gga gct ggc att tat ttt gct 4061
 Arg His Ala Tyr Ile Gly Gly Met Phe Gly Ala Gly Ile Tyr Phe Ala
 1050 1055 1060

gaa aac tct tcc aaa agc aat caa tat gta tat gga att gga gga ggt 4109
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 1065 1070 1075

act ggg tgt cca gtt cac aaa gac aga tct tgt tac att tgc cac agg 4157
 Thr Gly Cys Pro Val His Lys Asp Arg Ser Cys Tyr Ile Cys His Arg
 1080 1085 1090

cag ctg ctc ttt tgc cgg gta acc ttg gga aag tct ttc ctg cag ttc 4205
 Gln Leu Leu Phe Cys Arg Val Thr Leu Gly Lys Ser Phe Leu Gln Phe
 1095 1100 1105 1110

agt gca atg aaa atg gca cat tct cct cca ggt cat cac tca gtc act 4253
 Ser Ala Met Lys Met Ala His Ser Pro Pro Gly His His Ser Val Thr
 1115 1120 1125

ggt agg ccc agt gta aat ggc cta gca tta gct gaa tat gtt att tac 4301
 Gly Arg Pro Ser Val Asn Gly Leu Ala Leu Ala Glu Tyr Val Ile Tyr
 1130 1135 1140

aga gga gaa cag gct tat cct gag tat tta att act tac cag att atg 4349
 Arg Gly Glu Gln Ala Tyr Pro Glu Tyr Leu Ile Thr Tyr Gln Ile Met
 1145 1150 1155

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 Arg Pro Glu Gly Met Val Asp Gly
 1160 1165

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gacttgataa agctttaata atgtacagtg ttttctaaat atttcctggt ttttcagcac 4583

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acttgaacct tttatatgtt atgcattgat tctaacaac tgtaatgccc tcaacagaac 4703

taattttact aatacaatac tgtgttcttt aaaacacagc atttacactg aatacaattt 4763

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4992

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<212> PRT

<213> Homo sapiens

<400> 135

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35 40 45Val Asn Ser Arg Asp Thr Ala Gly Arg Lys Ser Thr Pro Leu His Phe
50 55 60Ala Ala Gly Phe Gly Arg Lys Asp Val Val Glu Tyr Leu Leu Gln Asn
65 70 75 80Gly Ala Asn Val Gln Ala Arg Asp Asp Gly Gly Leu Ile Pro Leu His
85 90 95Asn Ala Cys Ser Phe Gly His Ala Glu Val Val Asn Leu Leu Leu Arg
100 105 110His Gly Ala Asp Pro Asn Ala Arg Asp Asn Trp Asn Tyr Thr Pro Leu
115 120 125His Glu Ala Ala Ile Lys Gly Lys Ile Asp Val Cys Ile Val Leu Leu
130 135 140Gln His Gly Ala Glu Pro Thr Ile Arg Asn Thr Asp Gly Arg Thr Ala
145 150 155 160Leu Asp Leu Ala Asp Pro Ser Ala Lys Ala Val Leu Thr Gly Glu Tyr
165 170 175Lys Lys Asp Glu Leu Leu Glu Ser Ala Arg Ser Gly Asn Glu Glu Lys
180 185 190Met Met Ala Leu Leu Thr Pro Leu Asn Val Asn Cys His Ala Ser Asp
195 200 205Gly Arg Lys Ser Thr Pro Leu His Leu Ala Ala Gly Tyr Asn Arg Val
210 215 220Lys Ile Val Gln Leu Leu Gln His Gly Ala Asp Val His Ala Lys
225 230 235 240Asp Lys Gly Asp Leu Val Pro Leu His Asn Ala Cys Ser Tyr Gly His
245 250 255Tyr Glu Val Thr Glu Leu Leu Val Lys His Gly Ala Cys Val Asn Ala
260 265 270Met Asp Leu Trp Gln Phe Thr Pro Leu His Glu Ala Ala Ser Lys Asn
275 280 285Arg Val Glu Val Cys Ser Leu Leu Leu Ser Tyr Gly Ala Asp Pro Thr
290 295 300Leu Leu Asn Cys His Asn Lys Ser Ala Ile Asp Leu Ala Pro Thr Pro
305 310 315 320

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Gln Leu Lys Glu Arg Leu Ala Tyr Glu Phe Lys Gly His Ser Leu Leu
 325 330 335
 Gln Ala Ala Arg Glu Ala Asp Val Thr Arg Ile Lys Lys His Leu Ser
 340 345 350
 Leu Glu Met Val Asn Phe Lys His Pro Gln Thr His Glu Thr Ala Leu
 355 360 365
 His Cys Ala Ala Ala Ser Pro Tyr Pro Lys Arg Lys Gln Ile Cys Glu
 370 375 380
 Leu Leu Leu Arg Lys Gly Ala Asn Ile Asn Glu Lys Thr Lys Glu Phe
 385 390 395 400
 Leu Thr Pro Leu His Val Ala Ser Glu Lys Ala His Asn Asp Val Val
 405 410 415
 Glu Val Val Val Lys His Glu Ala Lys Val Asn Ala Leu Asp Asn Leu
 420 425 430
 Gly Gln Thr Ser Leu His Arg Ala Ala Tyr Cys Gly His Leu Gln Thr
 435 440 445
 Cys Arg Leu Leu Leu Ser Tyr Gly Cys Asp Pro Asn Ile Ile Ser Leu
 450 455 460
 Gln Gly Phe Thr Ala Leu Gln Met Gly Asn Glu Asn Val Gln Gln Leu
 465 470 475 480
 Leu Gln Glu Gly Ile Ser Leu Gly Asn Ser Glu Ala Asp Arg Gln Leu
 485 490 495
 Leu Glu Ala Ala Lys Ala Gly Asp Val Glu Thr Val Lys Lys Leu Cys
 500 505 510
 Thr Val Gln Ser Val Asn Cys Arg Asp Ile Glu Gly Arg Gln Ser Thr
 515 520 525
 Pro Leu His Phe Ala Ala Gly Tyr Asn Arg Val Ser Val Val Glu Tyr
 530 535 540
 Leu Leu Gln His Gly Ala Asp Val His Ala Lys Asp Lys Gly Gly Leu
 545 550 555 560
 Val Pro Leu His Asn Ala Cys Ser Tyr Gly His Tyr Glu Val Ala Glu
 565 570 575
 Leu Leu Val Lys His Gly Ala Val Val Asn Val Ala Asp Leu Trp Lys
 580 585 590
 Phe Thr Pro Leu His Glu Ala Ala Lys Gly Lys Tyr Glu Ile Cys
 595 600 605
 Lys Leu Leu Leu Gln His Gly Ala Asp Pro Thr Lys Lys Asn Arg Asp
 610 615 620
 Gly Asn Thr Pro Leu Asp Leu Val Lys Asp Gly Asp Thr Asp Ile Gln
 625 630 635 640
 Asp Leu Leu Arg Gly Asp Ala Ala Leu Leu Asp Ala Ala Lys Lys Gly
 645 650 655
 Cys Leu Ala Arg Val Lys Lys Leu Ser Ser Pro Asp Asn Val Asn Cys
 660 665 670
 Arg Asp Thr Gln Gly Arg His Ser Thr Pro Leu His Leu Ala Ala Gly
 675 680 685

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Tyr Asn Asn Leu Glu Val Ala Glu Tyr Leu Leu Gln His Gly Ala Asp
 690 695 700
 Val Asn Ala Gln Asp Lys Gly Gly Leu Ile Pro Leu His Asn Ala Ala
 705 710 715 720
 Ser Tyr Gly His Val Asp Val Ala Ala Leu Leu Ile Lys Tyr Asn Ala
 725 730 735
 Cys Val Asn Ala Thr Asp Lys Trp Ala Phe Thr Pro Leu His Glu Ala
 740 745 750
 Ala Gln Lys Gly Arg Thr Gln Leu Cys Ala Leu Leu Leu Ala His Gly
 755 760 765
 Ala Asp Pro Thr Leu Lys Asn Gln Glu Gly Gln Thr Pro Leu Asp Leu
 770 775 780
 Val Ser Ala Asp Asp Val Ser Ala Leu Leu Thr Ala Ala Met Pro Pro
 785 790 795 800
 Ser Ala Leu Pro Ser Cys Tyr Lys Pro Gln Val Leu Asn Gly Val Arg
 805 810 815
 Ser Pro Gly Ala Thr Ala Asp Ala Leu Ser Ser Gly Pro Ser Ser Pro
 820 825 830
 Ser Ser Leu Ser Ala Ala Ser Ser Leu Asp Asn Leu Ser Gly Ser Phe
 835 840 845
 Ser Glu Leu Ser Ser Val Val Ser Ser Ser Gly Thr Glu Gly Ala Ser
 850 855 860
 Ser Leu Glu Lys Lys Glu Val Pro Gly Val Asp Phe Ser Ile Thr Gln
 865 870 875 880
 Phe Val Arg Asn Leu Gly Leu Glu His Leu Met Asp Ile Phe Glu Arg
 885 890 895
 Glu Gln Ile Thr Leu Asp Val Leu Val Glu Met Gly His Lys Glu Leu
 900 905 910
 Lys Glu Ile Gly Ile Asn Ala Tyr Gly His Arg His Lys Leu Ile Lys
 915 920 925
 Gly Val Glu Arg Leu Ile Ser Gly Gln Gln Gly Leu Asn Pro Tyr Leu
 930 935 940
 Thr Leu Asn Thr Ser Gly Ser Gly Thr Ile Leu Ile Asp Leu Ser Pro
 945 950 955 960
 Asp Asp Lys Glu Phe Gln Ser Val Glu Glu Glu Met Gln Ser Thr Val
 965 970 975
 Arg Glu His Arg Asp Gly Gly His Ala Gly Gly Ile Phe Asn Arg Tyr
 980 985 990
 Asn Ile Leu Lys Ile Gln Lys Val Cys Asn Lys Lys Leu Trp Glu Arg
 995 1000 1005
 Tyr Thr His Arg Arg Lys Glu Val Ser Glu Glu Asn His Asn His Ala
 1010 1015 1020
 Asn Glu Arg Met Leu Phe His Gly Ser Pro Phe Val Asn Ala Ile Ile
 1025 1030 1035 1040
 His Lys Gly Phe Asp Glu Arg His Ala Tyr Ile Gly Gly Met Phe Gly
 1045 1050 1055

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Ala Gly Ile Tyr Phe Ala Glu Asn Ser Ser Lys Ser Asn Gln Tyr Val
 1060 1065 1070

Tyr Gly Ile Gly Gly Gly Thr Gly Cys Pro Val His Lys Asp Arg Ser
 1075 1080 1085

Cys Tyr Ile Cys His Arg Gln Leu Leu Phe Cys Arg Val Thr Leu Gly
 1090 1095 1100

Lys Ser Phe Leu Gln Phe Ser Ala Met Lys Met Ala His Ser Pro Pro
 1105 1110 1115 1120

Gly His His Ser Val Thr Gly Arg Pro Ser Val Asn Gly Leu Ala Leu
 1125 1130 1135

Ala Glu Tyr Val Ile Tyr Arg Gly Glu Gln Ala Tyr Pro Glu Tyr Leu
 1140 1145 1150

Ile Thr Tyr Gln Ile Met Arg Pro Glu Gly Met Val Asp Gly
 1155 1160 1165

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<211> 3045

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)..(3042)

<400> 136

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 Met Ala Glu Ser Ser Asp Lys Leu Tyr Arg Val Glu Tyr Ala Lys Ser
 1 5 10 15

ggg cgc gcc tct tgc aag aaa tgc agc gag agc atc ccc aag gac tcg 96
 Gly Arg Ala Ser Cys Lys Lys Cys Ser Glu Ser Ile Pro Lys Asp Ser
 20 25 30

ctc cgg atg gcc atc atg gtg cag tcg ccc atg ttt gat gga aaa gtc 144
 Leu Arg Met Ala Ile Met Val Gln Ser Pro Met Phe Asp Gly Lys Val
 35 40 45

cca cac tgg tac cac ttc tcc tgc ttc tgg aag gtg ggc cac tcc atc 192
 Pro His Trp Tyr His Phe Ser Cys Phe Trp Lys Val Gly His Ser Ile
 50 55 60

cgg cac cct gac gtt gag gtg gat ggg ttc tct gag ctt cgg tgg gat 240
 Arg His Pro Asp Val Glu Val Asp Gly Phe Ser Glu Leu Arg Trp Asp
 65 70 75 80

gac cag cag aaa gtc aag aag aca gcg gaa gct gga gga gtg aca ggc 288
 Asp Gln Gln Lys Val Lys Lys Thr Ala Glu Ala Gly Gly Val Thr Gly
 85 90 95

aaa ggc cag gat gga att ggt agc aag gca gag aag act ctg ggt gac 336
 Lys Gly Gln Asp Gly Ile Gly Ser Lys Ala Glu Lys Thr Leu Gly Asp
 100 105 110

ttt gca gca gag tat gcc aag tcc aac aga agt acg tgc aag ggg tgt 384
 Phe Ala Ala Glu Tyr Ala Lys Ser Asn Arg Ser Thr Cys Lys Gly Cys
 115 120 125

atg gag aag ata gaa aag ggc cag gtg cgc ctg tcc aag aag atg gtg 432
 Met Glu Lys Ile Glu Lys Gly Gln Val Arg Leu Ser Lys Lys Met Val
 130 135 140

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gac ccg gag aag cca cag cta ggc atg att gac cgc tgg tac cat cca	480
Asp Pro Glu Lys Pro Gln Leu Gly Met Ile Asp Arg Trp Tyr His Pro	
145 150 155 160	
ggc tgc ttt gtc aag aac agg gag gag ctg ggt ttc cgg ccc gag tac	528
Gly Cys Phe Val Lys Asn Arg Glu Glu Leu Gly Phe Arg Pro Glu Tyr	
165 170 175	
agt gcg agt cag ctc aag ggc ttc agc ctc ctt gct aca gag gat aaa	576
Ser Ala Ser Gln Leu Lys Gly Phe Ser Leu Leu Ala Thr Glu Asp Lys	
180 185 190	
gaa gcc ctg aag aag cag ctc cca gga gtc aag agt gaa gga aag aga	624
Glu Ala Leu Lys Lys Gln Leu Pro Gly Val Lys Ser Glu Gly Lys Arg	
195 200 205	
aaa ggc gat gag gtg gat gga gtg gat gaa gtg gcg aag aag aaa tct	672
Lys Gly Asp Glu Val Asp Gly Val Asp Glu Val Ala Lys Lys Lys Ser	
210 215 220	
aaa aaa gaa aaa gac aag gat agt aag ctt gaa aaa gcc cta aag gct	720
Lys Lys Glu Lys Asp Lys Asp Ser Lys Leu Glu Lys Ala Leu Lys Ala	
225 230 235 240	
cag aac gac ctg atc tgg aac atc aag gac gag cta aag aaa gtg tgt	768
Gln Asn Asp Leu Ile Trp Asn Ile Lys Asp Glu Leu Lys Lys Val Cys	
245 250 255	
tca act aat gac ctg aag gag cta ctc atc ttc aac aag cag caa gtg	816
Ser Thr Asn Asp Leu Lys Glu Leu Leu Ile Phe Asn Lys Gln Gln Val	
260 265 270	
cct tct ggg gag tcg gcg atc ttg gac cga gta gct gat ggc atg gtg	864
Pro Ser Gly Glu Ser Ala Ile Leu Asp Arg Val Ala Asp Gly Met Val	
275 280 285	
ttc ggt gcc ctc ctt ccc tgc gag gaa tgc tcg ggt cag ctg gtc ttc	912
Phe Gly Ala Leu Leu Pro Cys Glu Glu Cys Ser Gly Gln Leu Val Phe	
290 295 300	
aag agc gat gcc tat tac tgc act ggg gac gtc act gcc tgg acc aag	960
Lys Ser Asp Ala Tyr Cys Thr Gly Asp Val Thr Ala Trp Thr Lys	
305 310 315 320	
tgt atg gtc aag aca cag aca ccc aac cgg aag gag tgg gta acc cca	1008
Cys Met Val Lys Thr Gln Thr Pro Asn Arg Lys Glu Trp Val Thr Pro	
325 330 335	
aag gaa ttc cga gaa atc tct tac ctc aag aaa ttg aag gtt aaa aag	1056
Lys Glu Phe Arg Glu Ile Ser Tyr Leu Lys Lys Leu Lys Val Lys Lys	
340 345 350	
cag gac cgt ata ttc ccc cca gaa acc agc gcc tcc gtg gcg gcc acg	1104
Gln Asp Arg Ile Phe Pro Pro Glu Thr Ser Ala Ser Val Ala Ala Thr	
355 360 365	
cct ccg ccc tcc aca gcc tcg gct cct gct gct gtg aac tcc tct gct	1152
Pro Pro Pro Ser Thr Ala Ser Ala Pro Ala Ala Val Asn Ser Ser Ala	
370 375 380	
tca gca gat aag cca tta tcc aac atg aag atc ctg act ctc ggg aag	1200
Ser Ala Asp Lys Pro Leu Ser Asn Met Lys Ile Leu Thr Leu Gly Lys	
385 390 395 400	
ctg tcc cgg aac aag gat gaa gtg aag gcc atg att gag aaa ctc ggg	1248
Leu Ser Arg Asn Lys Asp Glu Val Lys Ala Met Ile Glu Lys Leu Gly	
405 410 415	

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ggg aag ttg acg ggg acg gcc aac aag gct tcc ctg tgc atc agc acc	1296
Gly Lys Leu Thr Gly Thr Ala Asn Lys Ala Ser Leu Cys Ile Ser Thr	
420 425 430	
aaa aag gag gtg gaa aag atg aat aag aag atg gag gaa gta aag gaa	1344
Lys Lys Glu Val Glu Lys Met Asn Lys Lys Met Glu Glu Val Lys Glu	
435 440 445	
gcc aac atc cga gtt gtg tct gag gac ttc ctc cag gac gtc tcc gcc	1392
Ala Asn Ile Arg Val Val Ser Glu Asp Phe Leu Gln Asp Val Ser Ala	
450 455 460	
tcc acc aag agc ctt cag gag ttg ttc tta gcg cac atc ttg tcc cct	1440
Ser Thr Lys Ser Leu Gln Glu Leu Phe Leu Ala His Ile Leu Ser Pro	
465 470 475 480	
tgg ggg gca gag gtg aag gca gag cct gtt gaa gtt gtg gcc cca aga	1488
Trp Gly Ala Glu Val Lys Ala Glu Pro Val Glu Val Val Ala Pro Arg	
485 490 495	
ggg aag tca ggg gct gcg ctc tcc aaa aaa agc aag ggc cag gtc aag	1536
Gly Lys Ser Gly Ala Ala Leu Ser Lys Lys Ser Lys Gly Gln Val Lys	
500 505 510	
gag gaa ggt atc aac aaa tct gaa aag aga atg aaa tta act ctt aaa	1584
Glu Glu Gly Ile Asn Lys Ser Glu Lys Arg Met Lys Leu Thr Leu Lys	
515 520 525	
gga gga gca gct gtg gat cct gat tct gga ctg gaa cac tct gcg cat	1632
Gly Gly Ala Ala Val Asp Pro Asp Ser Gly Leu Glu His Ser Ala His	
530 535 540	
gtc ctg gag aaa ggt ggg aag gtc ttc agt gcc acc ctt ggc ctg gtg	1680
Val Leu Glu Lys Gly Gly Lys Val Phe Ser Ala Thr Leu Gly Leu Val	
545 550 555 560	
gac atc gtt aaa gga acc aac tcc tac tac aag ctg cag ctt ctg gag	1728
Asp Ile Val Lys Gly Thr Asn Ser Tyr Lys Lys Leu Gln Leu Leu Glu	
565 570 575	
gac gac aag gaa aac agg tat tgg ata ttc agg tcc tgg ggc cgt gtg	1776
Asp Asp Lys Glu Asn Arg Tyr Trp Ile Phe Arg Ser Trp Gly Arg Val	
580 585 590	
ggt acg gtg atc ggt agc aac aaa ctg gaa cag atg ccg tcc aag gag	1824
Gly Thr Val Ile Gly Ser Asn Lys Leu Glu Gln Met Pro Ser Lys Glu	
595 600 605	
gat gcc att gag cag ttc atg aaa tta tat gaa gaa aaa acc ggg aac	1872
Asp Ala Ile Glu Gln Phe Met Lys Leu Tyr Glu Glu Lys Thr Gly Asn	
610 615 620	
gct tgg cac tcc aaa aat ttc acg aag tat ccc aaa aag ttt tac ccc	1920
Ala Trp His Ser Lys Asn Phe Thr Lys Tyr Pro Lys Lys Phe Tyr Pro	
625 630 635 640	
ctg gag att gac tat ggc cag gat gaa gag gca gtg aag aag ctc aca	1968
Leu Glu Ile Asp Tyr Gly Gln Asp Glu Glu Ala Val Lys Lys Leu Thr	
645 650 655	
gta aat cct ggc acc aag tcc aag ctc ccc aag cca gtt cag gac ctc	2016
Val Asn Pro Gly Thr Lys Ser Lys Leu Pro Lys Pro Val Gln Asp Leu	
660 665 670	
atc aag atg atc ttt gat gtg gaa agt atg aag aaa gcc atg gtg gag	2064
Ile Lys Met Ile Phe Asp Val Glu Ser Met Lys Lys Ala Met Val Glu	
675 680 685	

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tat gag atc gac ctt cag aag atg ccc ttg ggg aag ctg agc aaa agg	2112
Tyr Glu Ile Asp Leu Gln Lys Met Pro Leu Gly Lys Leu Ser Lys Arg	
690 695 700	
cag atc cag gcc gca tac tcc atc ctc agt gag gtc cag cag gcg gtg	2160
Gln Ile Gln Ala Ala Tyr Ser Ile Leu Ser Gln Val Gln Gln Ala Val	
705 710 715 720	
tct cag ggc agc agc gac tct cag atc ctg gat ctc tca aat cgc ttt	2208
Ser Gln Gly Ser Ser Asp Ser Gln Ile Leu Asp Leu Ser Asn Arg Phe	
725 730 735	
tac acc ctg atc ccc cac gac ttt ggg atg aag aag cct ccg ctc ctg	2256
Tyr Thr Leu Ile Pro His Asp Phe Gly Met Lys Lys Pro Pro Leu Leu	
740 745 750	
aac aat gca gac agt gtg cag gcc aag gtg gaa atg ctt gac aac ctg	2304
Asn Asn Ala Asp Ser Val Gln Ala Lys Val Glu Met Leu Asp Asn Leu	
755 760 765	
ctg gac atc gag gtg gcc tac agt ctg ctc agg gga ggg tct gat gat	2352
Leu Asp Ile Glu Val Ala Tyr Ser Leu Leu Arg Gly Gly Ser Asp Asp	
770 775 780	
agc agc aag gat ccc atc gat gtc aac tat gag aag ctc aaa act gac	2400
Ser Ser Lys Asp Pro Ile Asp Val Asn Tyr Glu Lys Leu Lys Thr Asp	
785 790 795 800	
att aag gtg gtt gac aga gat tct gaa gaa gcc gag atc atc agg aag	2448
Ile Lys Val Val Asp Arg Asp Ser Glu Glu Ala Glu Ile Ile Arg Lys	
805 810 815	
tat gtt aag aac act cat gca acc aca cac agt gcg tat gac ttg gaa	2496
Tyr Val Lys Asn Thr His Ala Thr Thr His Ser Ala Tyr Asp Leu Glu	
820 825 830	
gtc atc gat atc ttt aag ata gag cgt gaa ggc gaa tgc cag cgt tac	2544
Val Ile Asp Ile Phe Lys Ile Glu Arg Glu Gly Glu Cys Gln Arg Tyr	
835 840 845	
aag ccc ttt aag cag ctt cat aac cga aga ttg ctg tgg cac ggg tcc	2592
Lys Pro Phe Lys Gln Leu His Asn Arg Arg Leu Leu Trp His Gly Ser	
850 855 860	
agg acc acc aac ttt gct ggg atc ctg tcc cag ggt ctt cgg ata gcc	2640
Arg Thr Thr Asn Phe Ala Gly Ile Leu Ser Gln Gly Leu Arg Ile Ala	
865 870 875 880	
ccg cct gaa gcg ccc gtg aca ggc tac atg ttt ggt aaa ggg atc tat	2688
Pro Pro Glu Ala Pro Val Thr Gly Tyr Met Phe Gly Lys Gly Ile Tyr	
885 890 895	
ttc gct gac atg gtc tcc aag agt gcc aac tac tac cat acg tct cag	2736
Phe Ala Asp Met Val Ser Lys Ser Ala Asn Tyr Tyr His Thr Ser Gln	
900 905 910	
gga gac cca ata ggc tta atc ctg ttg gga gaa gtt gcc ctt gga aac	2784
Gly Asp Pro Ile Gly Leu Ile Leu Leu Gly Glu Val Ala Leu Gly Asn	
915 920 925	
atg tat gaa ctg aag cac gct tca cat atc agc agg tta ccc aag ggc	2832
Met Tyr Glu Leu Lys His Ala Ser His Ile Ser Arg Leu Pro Lys Gly	
930 935 940	
aag cac agt gtc aaa ggt ttg ggc aaa act acc cct gat cct tca gct	2880
Lys His Ser Val Lys Gly Leu Gly Lys Thr Thr Pro Asp Pro Ser Ala	
945 950 955 960	

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aac att agt ctg gat ggt gta gac gtt cct ctt ggg acc ggg att tca 2928
 Asn Ile Ser Leu Asp Gly Val Asp Val Pro Leu Gly Thr Gly Ile Ser
 965 970 975

tct ggt gtg ata gac acc tct cta cta tat aac gag tac att gtc tat 2976
 Ser Gly Val Ile Asp Thr Ser Leu Tyr Asn Glu Tyr Ile Val Tyr
 980 985 990

gat att gct cag gta aat ctg aag tat ctg ctg aaa ctg aaa ttc aat 3024
 Asp Ile Ala Gln Val Asn Leu Lys Tyr Leu Leu Lys Leu Lys Phe Asn
 995 1000 1005

ttt aag acc tcc ctg tgg taa 3045
 Phe Lys Thr Ser Leu Trp
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<210> 137

<211> 1014

<212> PRT

<213> Homo sapiens

<400> 137

Met Ala Glu Ser Ser Asp Lys Leu Tyr Arg Val Glu Tyr Ala Lys Ser
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Gly Arg Ala Ser Cys Lys Lys Cys Ser Glu Ser Ile Pro Lys Asp Ser
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Leu Arg Met Ala Ile Met Val Gln Ser Pro Met Phe Asp Gly Lys Val
 35 40 45

Pro His Trp Tyr His Phe Ser Cys Phe Trp Lys Val Gly His Ser Ile
 50 55 60

Arg His Pro Asp Val Glu Val Asp Gly Phe Ser Glu Leu Arg Trp Asp
 65 70 75 80

Asp Gln Gln Lys Val Lys Lys Thr Ala Glu Ala Gly Gly Val Thr Gly
 85 90 95

Lys Gly Gln Asp Gly Ile Gly Ser Lys Ala Glu Lys Thr Leu Gly Asp
 100 105 110

Phe Ala Ala Glu Tyr Ala Lys Ser Asn Arg Ser Thr Cys Lys Gly Cys
 115 120 125

Met Glu Lys Ile Glu Lys Gly Gln Val Arg Leu Ser Lys Lys Met Val
 130 135 140

Asp Pro Glu Lys Pro Gln Leu Gly Met Ile Asp Arg Trp Tyr His Pro
 145 150 155 160

Gly Cys Phe Val Lys Asn Arg Glu Glu Leu Gly Phe Arg Pro Glu Tyr
 165 170 175

Ser Ala Ser Gln Leu Lys Gly Phe Ser Leu Leu Ala Thr Glu Asp Lys
 180 185 190

Glu Ala Leu Lys Lys Gln Leu Pro Gly Val Lys Ser Glu Gly Lys Arg
 195 200 205

Lys Gly Asp Glu Val Asp Gly Val Asp Glu Val Ala Lys Lys Lys Ser
 210 215 220

Lys Lys Glu Lys Asp Lys Asp Ser Lys Leu Glu Lys Ala Leu Lys Ala
 225 230 235 240

Gln Asn Asp Leu Ile Trp Asn Ile Lys Asp Glu Leu Lys Lys Val Cys
 245 250 255

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Ser Thr Asn Asp Leu Lys Glu Leu Leu Ile Phe Asn Lys Gln Gln Val
 260 265 270
 Pro Ser Gly Glu Ser Ala Ile Leu Asp Arg Val Ala Asp Gly Met Val
 275 280 285
 Phe Gly Ala Leu Leu Pro Cys Glu Glu Cys Ser Gly Gln Leu Val Phe
 290 295 300
 Lys Ser Asp Ala Tyr Tyr Cys Thr Gly Asp Val Thr Ala Trp Thr Lys
 305 310 315 320
 Cys Met Val Lys Thr Gln Thr Pro Asn Arg Lys Glu Trp Val Thr Pro
 325 330 335
 Lys Glu Phe Arg Glu Ile Ser Tyr Leu Lys Lys Leu Lys Val Lys Lys
 340 345 350
 Gln Asp Arg Ile Phe Pro Pro Glu Thr Ser Ala Ser Val Ala Ala Thr
 355 360 365
 Pro Pro Pro Ser Thr Ala Ser Ala Pro Ala Ala Val Asn Ser Ser Ala
 370 375 380
 Ser Ala Asp Lys Pro Leu Ser Asn Met Lys Ile Leu Thr Leu Gly Lys
 385 390 395 400
 Leu Ser Arg Asn Lys Asp Glu Val Lys Ala Met Ile Glu Lys Leu Gly
 405 410 415
 Gly Lys Leu Thr Gly Thr Ala Asn Lys Ala Ser Leu Cys Ile Ser Thr
 420 425 430
 Lys Lys Glu Val Glu Lys Met Asn Lys Lys Met Glu Glu Val Lys Glu
 435 440 445
 Ala Asn Ile Arg Val Val Ser Glu Asp Phe Leu Gln Asp Val Ser Ala
 450 455 460
 Ser Thr Lys Ser Leu Gln Glu Leu Phe Leu Ala His Ile Leu Ser Pro
 465 470 475 480
 Trp Gly Ala Glu Val Lys Ala Glu Pro Val Glu Val Val Ala Pro Arg
 485 490 495
 Gly Lys Ser Gly Ala Ala Leu Ser Lys Lys Ser Lys Gly Gln Val Lys
 500 505 510
 Glu Glu Gly Ile Asn Lys Ser Glu Lys Arg Met Lys Leu Thr Leu Lys
 515 520 525
 Gly Gly Ala Ala Val Asp Pro Asp Ser Gly Leu Glu His Ser Ala His
 530 535 540
 Val Leu Glu Lys Gly Gly Lys Val Phe Ser Ala Thr Leu Gly Leu Val
 545 550 555 560
 Asp Ile Val Lys Gly Thr Asn Ser Tyr Tyr Lys Leu Gln Leu Leu Glu
 565 570 575
 Asp Asp Lys Glu Asn Arg Tyr Trp Ile Phe Arg Ser Trp Gly Arg Val
 580 585 590
 Gly Thr Val Ile Gly Ser Asn Lys Leu Glu Gln Met Pro Ser Lys Glu
 595 600 605
 Asp Ala Ile Glu Gln Phe Met Lys Leu Tyr Glu Glu Lys Thr Gly Asn
 610 615 620

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Ala Trp His Ser Lys Asn Phe Thr Lys Tyr Pro Lys Lys Phe Tyr Pro
 625 630 635 640
 Leu Glu Ile Asp Tyr Gly Gln Asp Glu Glu Ala Val Lys Lys Leu Thr
 645 650 655
 Val Asn Pro Gly Thr Lys Ser Lys Leu Pro Lys Pro Val Gln Asp Leu
 660 665 670
 Ile Lys Met Ile Phe Asp Val Glu Ser Met Lys Lys Ala Met Val Glu
 675 680 685
 Tyr Glu Ile Asp Leu Gln Lys Met Pro Leu Gly Lys Leu Ser Lys Arg
 690 695 700
 Gln Ile Gln Ala Ala Tyr Ser Ile Leu Ser Glu Val Gln Gln Ala Val
 705 710 715 720
 Ser Gln Gly Ser Ser Asp Ser Gln Ile Leu Asp Leu Ser Asn Arg Phe
 725 730 735
 Tyr Thr Leu Ile Pro His Asp Phe Gly Met Lys Lys Pro Pro Leu Leu
 740 745 750
 Asn Asn Ala Asp Ser Val Gln Ala Lys Val Glu Met Leu Asp Asn Leu
 755 760 765
 Leu Asp Ile Glu Val Ala Tyr Ser Leu Leu Arg Gly Gly Ser Asp Asp
 770 775 780
 Ser Ser Lys Asp Pro Ile Asp Val Asn Tyr Glu Lys Leu Lys Thr Asp
 785 790 795 800
 Ile Lys Val Val Asp Arg Asp Ser Glu Glu Ala Glu Ile Ile Arg Lys
 805 810 815
 Tyr Val Lys Asn Thr His Ala Thr Thr His Ser Ala Tyr Asp Leu Glu
 820 825 830
 Val Ile Asp Ile Phe Lys Ile Glu Arg Glu Gly Glu Cys Gln Arg Tyr
 835 840 845
 Lys Pro Phe Lys Gln Leu His Asn Arg Arg Leu Leu Trp His Gly Ser
 850 855 860
 Arg Thr Thr Asn Phe Ala Gly Ile Leu Ser Gln Gly Leu Arg Ile Ala
 865 870 875 880
 Pro Pro Glu Ala Pro Val Thr Gly Tyr Met Phe Gly Lys Gly Ile Tyr
 885 890 895
 Phe Ala Asp Met Val Ser Lys Ser Ala Asn Tyr Tyr His Thr Ser Gln
 900 905 910
 Gly Asp Pro Ile Gly Leu Ile Leu Leu Gly Glu Val Ala Leu Gly Asn
 915 920 925
 Met Tyr Glu Leu Lys His Ala Ser His Ile Ser Arg Leu Pro Lys Gly
 930 935 940
 Lys His Ser Val Lys Gly Leu Gly Lys Thr Thr Pro Asp Pro Ser Ala
 945 950 955 960
 Asn Ile Ser Leu Asp Gly Val Asp Val Pro Leu Gly Thr Gly Ile Ser
 965 970 975
 Ser Gly Val Ile Asp Thr Ser Leu Leu Tyr Asn Glu Tyr Ile Val Tyr
 980 985 990

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Asp Ile Ala Gln Val Asn Leu Lys Tyr Leu Leu Lys Leu Lys Phe Asn
 995 1000 1005

Phe Lys Thr Ser Leu Trp
 1010

<210> 138
 <211> 5482
 <212> DNA
 <213> *Drosophila melanogaster*

<220>
 <221> CDS
 <222> (474)..(4016)

<400> 138
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 gctttggagg ccaagtacca gggagctagt cccagagttg gtcgcagtc cagtaaaaac 120
 gaatcgtagc caaccgcgat ccttgcaacc gtgctgtgtc gaaccaaaga aatcctattg 180
 attttgggtc tgcaattgtg cattaaatat taagcaaaaa cgagggctgg tcgcgtggca 240
 gccagtgcca aattgttgct cctgcggcat aggcaggaca cctggatata ggatgcgggc 300
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 agaactggac tgggagtggg aaacccgaaa gccactgaa tattgcgctt gttttttgtt 420
 gcctatTTTT ttcggggcgt gtgtgtgccg aagcgtagca aacaagcaca aca atg 476
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 gcc aac agc agc cga agt cgg gcc att ttg agc gtt aat ctc gat gcg 524
 Ala Asn Ser Ser Arg Ser Arg Ala Ile Leu Ser Val Asn Leu Asp Ala
 5 10 15
 gtc atg gcc aac gat ccg ctg agg gag ctc tcc gag gcc tgc aaa acg 572
 Val Met Ala Asn Asp Pro Leu Arg Glu Leu Ser Glu Ala Cys Lys Thr
 20 25 30
 ggc gag atc gcc aag gtg aag aag cta ata acg cct cag acc gtg aac 620
 Gly Glu Ile Ala Lys Val Lys Lys Leu Ile Thr Pro Gln Thr Val Asn
 35 40 45
 gcc agg gat acg gcg gga cgc aaa tcc aca cca ttg cat ttc gca gcg 668
 Ala Arg Asp Thr Ala Gly Arg Lys Ser Thr Pro Leu His Phe Ala Ala
 50 55 60 65
 ggt tat gga cgc cgg gaa gtg gtt gaa ttc ctg ctg aac agc ggc gcc 716
 Gly Tyr Gly Arg Arg Glu Val Val Glu Phe Leu Leu Asn Ser Gly Ala
 70 75 80
 tcc ata cag gcg tgt gac gag ggt ggg ctg cac ccg ctg cac aac tgt 764
 Ser Ile Gln Ala Cys Asp Glu Gly Gly Leu His Pro Leu His Asn Cys
 85 90 95
 tgc tcc ttt ggc cac gcc gag gta gtt cga ttg ttg ctg aag gca ggt 812
 Cys Ser Phe Gly His Ala Glu Val Val Arg Leu Leu Leu Lys Ala Gly
 100 105 110
 gcc agt cca aac acc acc gac aac tgg aac tac acg cca ttg cac gag 860
 Ala Ser Pro Asn Thr Thr Asp Asn Trp Asn Tyr Thr Pro Leu His Glu
 115 120 125

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gcg gcc agc aag ggc aag gtg gat gtg tgc ctg gct ctg ttg cag cat Ala Ala Ser Lys Gly Lys Val Asp Val Cys Leu Ala Leu Leu Gln His 130 135 140 145	908
ggc gca aac cat acg atc cgc aac tcg gag cag aag aca cca ctg gag Gly Ala Asn His Thr Ile Arg Asn Ser Glu Gln Lys Thr Pro Leu Glu 150 155 160	956
ctg gcg gac gag gcg acg cgt ccc gta ttg acc ggc gaa tat cga aag Leu Ala Asp Glu Ala Thr Arg Pro Val Leu Thr Gly Glu Tyr Arg Lys 165 170 175	1004
gat gag ctg ctt gaa gcc gca cgc tcg ggg gcc gag gat cgc ctg ctg Asp Glu Leu Leu Glu Ala Ala Arg Ser Gly Ala Glu Asp Arg Leu Leu 180 185 190	1052
gcc cta ctc acg cca ctc aat gtc aac tgt cat gcc agc gat gga cga Ala Leu Leu Thr Pro Leu Asn Val Asn Cys His Ala Ser Asp Gly Arg 195 200 205	1100
cgc tca acg ccg ctc cat ctg gca gcg ggc tac aat cgg atc ggc atc Arg Ser Thr Pro Leu His Leu Ala Ala Gly Tyr Asn Arg Ile Gly Ile 210 215 220 225	1148
gtg gaa att ctg ctg gcc aac gga gcg gat gta cat gct aag gac aag Val Glu Ile Leu Leu Ala Asn Gly Ala Asp Val His Ala Lys Asp Lys 230 235 240	1196
ggc ggt ctg gtg ccg ctg cac aat gcc tgc tcc tac gga cac ttc gat Gly Gly Leu Val Pro Leu His Asn Ala Cys Ser Tyr Gly His Phe Asp 245 250 255	1244
gtg acc aag ctg ctt atc cag gcg ggc gcc aat gtc aac gcc aac gat Val Thr Lys Leu Leu Ile Gln Ala Gly Ala Asn Val Asn Ala Asn Asp 260 265 270	1292
ctg tgg gcc ttt acg ccg ctc cac gag gcc gcc tcc aaa agt cgc gtc Leu Trp Ala Phe Thr Pro Leu His Glu Ala Ala Ser Lys Ser Arg Val 275 280 285	1340
gag gtc tgc agc ctg ctg ctc agt cgt gga gcg gat ccc acc ctc cta Glu Val Cys Ser Leu Leu Ser Arg Gly Ala Asp Pro Thr Leu Leu 290 295 300 305	1388
aac tgc cac agc aag tcg gcc atc gat gcg gcg ccc acc agg gag ctg Asn Cys His Ser Lys Ser Ala Ile Asp Ala Ala Pro Thr Arg Glu Leu 310 315 320	1436
aga gag cgg att gcc ttt gaa tac aag ggt cac tgc ctg ctg gac gcc Arg Glu Arg Ile Ala Phe Glu Tyr Lys Gly His Cys Leu Leu Asp Ala 325 330 335	1484
tgt cga aag tgt gat gtg tcc cgt gcc aag aag ctg gta tgc gca gag Cys Arg Lys Cys Asp Val Ser Arg Ala Lys Lys Leu Val Cys Ala Glu 340 345 350	1532
att gtt aac ttc gtg cat cca tat aca gga gac act ccg ctc cac ctg Ile Val Asn Phe Val His Pro Tyr Thr Gly Asp Thr Pro Leu His Leu 355 360 365	1580
gcc gtt gtc agt ccg gat ggg aag cgc aag cag ctg atg gaa ctg ctg Ala Val Val Ser Pro Asp Gly Lys Arg Lys Gln Leu Met Glu Leu Leu 370 375 380 385	1628
acc aga aag gga tcc ttg ctg aac gag aaa aac aag gct ttc ctc acg Thr Arg Lys Gly Ser Leu Leu Asn Glu Lys Asn Lys Ala Phe Leu Thr 390 395 400	1676

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Pro Leu His Leu Ala Ala Glu Leu Leu His Tyr Asp Ala Met Glu Val	
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ctg cta aag cag ggc gcc aag gtt aat gca ttg gac agt ctt gga caa	1772
Leu Leu Lys Gln Gly Ala Lys Val Asn Ala Leu Asp Ser Leu Gly Gln	
420 425 430	
acg cca ctg cat cgg tgc gcc cgt gat gag caa gcg gtg cga ctg ctg	1820
Thr Pro Leu His Arg Cys Ala Arg Asp Glu Gln Ala Val Arg Leu Leu	
435 440 445	
ctc tcg tac gca gcg gac acg aat atc gtt tcc ctt gag gga ctt acg	1868
Leu Ser Tyr Ala Ala Asp Thr Asn Ile Val Ser Leu Glu Gly Leu Thr	
450 455 460 465	
gcc gct caa ttg gcc tcg gac agc gtg ctg aag ctg ctc aag aat cct	1916
Ala Ala Gln Leu Ala Ser Asp Ser Val Leu Lys Leu Leu Lys Asn Pro	
470 475 480	
ccg gac agt gag aca cat tta ctg gag gca gcc aag gcg gga gat ctg	1964
Pro Asp Ser Glu Thr His Leu Leu Glu Ala Ala Lys Ala Gly Asp Leu	
485 490 495	
gac act gtg cgc cgt ata gtg ctc aac aat ccg att tcg gtc aat tgc	2012
Asp Thr Val Arg Arg Ile Val Leu Asn Asn Pro Ile Ser Val Asn Cys	
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cgg gat ttg gac gga cga cat tcc aca cct ttg cac ttt gct gct ggg	2060
Arg Asp Leu Asp Gly Arg His Ser Thr Pro Leu His Phe Ala Ala Gly	
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Phe Asn Arg Val Pro Val Val Gln Phe Leu Leu Glu His Gly Ala Glu	
530 535 540 545	
gtt tat gcg gct gac aag ggc gga ctg gtg ccc ctg cac aat gcc tgc	2156
Val Tyr Ala Ala Asp Lys Gly Gly Leu Val Pro Leu His Asn Ala Cys	
550 555 560	
tct tat ggg cac tat gag gta acc gaa ctg ctg gtc aag cac gga gcc	2204
Ser Tyr Gly His Tyr Glu Val Thr Glu Leu Leu Val Lys His Gly Ala	
565 570 575	
aat gta aat gta tcg gat ttg tgg aag ttt act cct ctt cat gaa gct	2252
Asn Val Asn Val Ser Asp Leu Trp Lys Phe Thr Pro Leu His Glu Ala	
580 585 590	
gcc gcc aag gga aag tat gat att tgc aag ctg ctc ttg aaa cat ggc	2300
Ala Ala Lys Gly Lys Tyr Asp Ile Cys Lys Leu Leu Lys His Gly	
595 600 605	
gct gat cca atg aag aag aat cgg gat ggc gcg aca cca gcg gat ttg	2348
Ala Asp Pro Met Lys Lys Asn Arg Asp Gly Ala Thr Pro Ala Asp Leu	
610 615 620 625	
gtt aag gaa tct gat cac gat gtt gca gag ctg ctg aga gga ccg tcc	2396
Val Lys Glu Ser Asp His Asp Val Ala Glu Leu Leu Arg Gly Pro Ser	
630 635 640	
gct ctg cta gac gca gca aag aaa gga aac ttg gca gcg gta cag cga	2444
Ala Leu Leu Asp Ala Ala Lys Lys Gly Asn Leu Ala Arg Val Gln Arg	
645 650 655	
ttg gtt aca ccg gaa tcc att aat tgc cgg gac gcg cag ggc agg aat	2492
Leu Val Thr Pro Glu Ser Ile Asn Cys Arg Asp Ala Gln Gly Arg Asn	
660 665 670	

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tcc aca cca ctt cac ctg gcc gcc gga tat aac aac ttt gag tgt gcc	2540
Ser Thr Pro Leu His Leu Ala Ala Gly Tyr Asn Asn Phe Glu Cys Ala	
675 680 685	
gag tac ctt ctg gag aat gga gcc gat gtt aat gca cag gac aag ggg	2588
Glu Tyr Leu Leu Glu Asn Gly Ala Asp Val Asn Ala Gln Asp Lys Gly	
690 695 700 705	
gga cta ata cct ctg cac aat gcc agc agc tat ggg cat ttg gat att	2636
Gly Leu Ile Pro Leu His Asn Ala Ser Ser Tyr Gly His Leu Asp Ile	
710 715 720	
gcg gca ctg cta att aag cac aag acg gtt gtc aat gcg aca gat aaa	2684
Ala Ala Leu Leu Ile Lys His Lys Thr Val Val Asn Ala Thr Asp Lys	
725 730 735	
tgg gga ttc aca ccg ctc cac gag gct gca cag aag ggg cgc act caa	2732
Trp Gly Phe Thr Pro Leu His Glu Ala Ala Gln Lys Gly Arg Thr Gln	
740 745 750	
ttg tgc tcg ctc ttg ttg gcc cac ggt gcc gat gcc tat atg aaa aac	2780
Leu Cys Ser Leu Leu Leu Ala His Gly Ala Asp Ala Tyr Met Lys Asn	
755 760 765	
cag gag ggg cag acg ccc att gag ttg gcc acg gca gat gat gtt aag	2828
Gln Glu Gly Gln Thr Pro Ile Glu Leu Ala Thr Ala Asp Asp Val Lys	
770 775 780 785	
tgc ttg ctc cag gac gcg atg gcc acc tcg ttg agt caa cag gcg ttg	2876
Cys Leu Leu Gln Asp Ala Met Ala Thr Ser Leu Ser Gln Gln Ala Leu	
790 795 800	
agt gct tcc acg caa tcg ctg aca agc agt tcc ccg gca cca gat gca	2924
Ser Ala Ser Thr Gln Ser Leu Thr Ser Ser Ser Pro Ala Pro Asp Ala	
805 810 815	
act gct gct gcg gct ccg ggc aca tct tca tcg tcc tca tcc gca atc	2972
Thr Ala Ala Ala Pro Gly Thr Ser Ser Ser Ser Ser Ser Ala Ile	
820 825 830	
cta tcg ccc acc acg gaa acg gtg ttg ctg ccc acc ggt gcc tcc atg	3020
Leu Ser Pro Thr Thr Glu Thr Val Leu Leu Pro Thr Gly Ala Ser Met	
835 840 845	
att ctg agt gtt cct gtt cca ctt cca ctg tcc agt agc acg cgc atc	3068
Ile Leu Ser Val Pro Val Pro Leu Pro Leu Ser Ser Ser Thr Arg Ile	
850 855 860 865	
agt ccc gcc caa gga gca gag gcc aat ggg gct gag ggc tcc tct tcg	3116
Ser Pro Ala Gln Gly Ala Glu Ala Asn Gly Ala Glu Gly Ser Ser Ser	
870 875 880	
gat gat cta ctg ccg gat gcg gat acc ata aca aat gtg tcc gga ttc	3164
Asp Asp Leu Leu Pro Asp Ala Asp Thr Ile Thr Asn Val Ser Gly Phe	
885 890 895	
cta agc agc cag cag ctg cat cat cta atc gaa ctg ttc gag cgc gaa	3212
Leu Ser Ser Gln Gln Leu His His Leu Ile Glu Leu Phe Glu Arg Glu	
900 905 910	
caa atc acc ttg gac att cta gcc gag atg ggc cac gac gat ctc aag	3260
Gln Ile Thr Leu Asp Ile Leu Ala Glu Met Gly His Asp Asp Leu Lys	
915 920 925	
cag gtg ggc gtc tcc gcc tac ggc ttc cgc cac aag ata ctc aag gga	3308
Gln Val Gly Val Ser Ala Tyr Gly Phe Arg His Lys Ile Leu Lys Gly	
930 935 940 945	

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atc gcc cag ctg agg tcc acc aca ggc att ggt aac aac gtg aat cta 3356
 Ile Ala Gln Leu Arg Ser Thr Thr Gly Ile Gly Asn Asn Val Asn Leu
 950 955 960

tgc aca ttg ttg gtg gac ttg ctg ccg gac gat aag gag ttt gtg gcc 3404
 Cys Thr Leu Leu Val Asp Leu Leu Pro Asp Asp Lys Glu Phe Val Ala
 965 970 975

gtc gag gag gag atg cag gcc acg att cgt gaa cat cgt gat aat gga 3452
 Val Glu Glu Glu Met Gln Ala Thr Ile Arg Glu His Arg Asp Asn Gly
 980 985 990

cag gct gga ggt tat ttc act cga tat aac atc att cgg gtg caa aag 3500
 Gln Ala Gly Gly Tyr Phe Thr Arg Tyr Asn Ile Ile Arg Val Gln Lys
 995 1000 1005

gta caa aat cga aag ctg tgg gag cgt tat gct cat cga cgg caa gag 3548
 Val Gln Asn Arg Lys Leu Trp Glu Arg Tyr Ala His Arg Arg Gln Glu
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atc gcc gag gag aat ttc ctg cag tcc aac gag cgt atg ctc ttc cac 3596
 Ile Ala Glu Glu Asn Phe Leu Gln Ser Asn Glu Arg Met Leu Phe His
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 Gly Ser Pro Phe Ile Asn Ala Ile Val Gln Arg Gly Phe Asp Glu Arg
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cac gcc tac att ggc ggc atg ttt ggg gct ggc att tat ttc gcc gag 3692
 His Ala Tyr Ile Gly Gly Met Phe Gly Ala Gly Ile Tyr Phe Ala Glu
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cat agc tcg aaa agc aac cag tat gtg tac gga att ggc ggc ggc att 3740
 His Ser Ser Lys Ser Asn Gln Tyr Val Tyr Gly Ile Gly Gly Gly Ile
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 Gly Cys Pro Ser His Lys Asp Lys Ser Cys Tyr Val Cys Pro Arg Gln
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 Ala Met Lys Met Ala His Ala Pro Pro Gly His His Ser Val Val Gly
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aga ccc tcg gcg ggt ggc ttg cat ttc gcc gaa tac gtt gtc tat cgg 3932
 Arg Pro Ser Ala Gly Gly Leu His Phe Ala Glu Tyr Val Val Tyr Arg
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ggc gaa cag tct tat ccg gag tac ttg ata acc tac caa atc gtc aag 3980
 Gly Glu Gln Ser Tyr Pro Glu Tyr Leu Ile Thr Tyr Gln Ile Val Lys
 1155 1160 1165

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 Pro Asp Asp Ser Ser Ser Gly Thr Glu Asp Thr Arg
 1170 1175 1180

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aacaaccgca gcagcaacag cagcagcagc cgcaaccaca acaacagcag aaggcaccac 4146

tgccggtgcc accgccacaa cagcagacct cagctccagt tgccaagagg cggccgaaac 4206

atgccaaacc atcgctgcag ttgcagtatc agccctatca gccccagcac cacccggttg 4266

ttgcaaccgc cgctgctgtg accaccaccc aaccttcgcc cgctggcggtt ttgcgacaca 4326

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<210> 139

<211> 1181

<212> PRT

<213> *Drosophila melanogaster*

<400> 139

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Ala	Val	Met	Ala	Asn	Asp	Pro	Leu	Arg	Glu	Leu	Ser	Glu	Ala	Cys	Lys
			20					25					30		
Thr	Gly	Glu	Ile	Ala	Lys	Val	Lys	Lys	Leu	Ile	Thr	Pro	Gln	Thr	Val
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Asn	Ala	Arg	Asp	Thr	Ala	Gly	Arg	Lys	Ser	Thr	Pro	Leu	His	Phe	Ala
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Ala	Gly	Tyr	Gly	Arg	Arg	Glu	Val	Val	Glu	Phe	Leu	Leu	Asn	Ser	Gly
65				70					75					80	
Ala	Ser	Ile	Gln	Ala	Cys	Asp	Glu	Gly	Gly	Leu	His	Pro	Leu	His	Asn
			85					90					95		
Cys	Cys	Ser	Phe	Gly	His	Ala	Glu	Val	Val	Arg	Leu	Leu	Leu	Lys	Ala
			100				105						110		
Gly	Ala	Ser	Pro	Asn	Thr	Thr	Asp	Asn	Trp	Asn	Tyr	Thr	Pro	Leu	His
	115						120					125			

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Glu Ala Ala Ser Lys Gly Lys Val Asp Val Cys Leu Ala Leu Leu Gln
 130 135 140
 His Gly Ala Asn His Thr Ile Arg Asn Ser Glu Gln Lys Thr Pro Leu
 145 150 155 160
 Glu Leu Ala Asp Glu Ala Thr Arg Pro Val Leu Thr Gly Glu Tyr Arg
 165 170 175
 Lys Asp Glu Leu Leu Glu Ala Ala Arg Ser Gly Ala Glu Asp Arg Leu
 180 185 190
 Leu Ala Leu Leu Thr Pro Leu Asn Val Asn Cys His Ala Ser Asp Gly
 195 200 205
 Arg Arg Ser Thr Pro Leu His Leu Ala Ala Gly Tyr Asn Arg Ile Gly
 210 215 220
 Ile Val Glu Ile Leu Leu Ala Asn Gly Ala Asp Val His Ala Lys Asp
 225 230 235 240
 Lys Gly Gly Leu Val Pro Leu His Asn Ala Cys Ser Tyr Gly His Phe
 245 250 255
 Asp Val Thr Lys Leu Leu Ile Gln Ala Gly Ala Asn Val Asn Ala Asn
 260 265 270
 Asp Leu Trp Ala Phe Thr Pro Leu His Glu Ala Ala Ser Lys Ser Arg
 275 280 285
 Val Glu Val Cys Ser Leu Leu Leu Ser Arg Gly Ala Asp Pro Thr Leu
 290 295 300
 Leu Asn Cys His Ser Lys Ser Ala Ile Asp Ala Ala Pro Thr Arg Glu
 305 310 315 320
 Leu Arg Glu Arg Ile Ala Phe Glu Tyr Lys Gly His Cys Leu Leu Asp
 325 330 335
 Ala Cys Arg Lys Cys Asp Val Ser Arg Ala Lys Lys Leu Val Cys Ala
 340 345 350
 Glu Ile Val Asn Phe Val His Pro Tyr Thr Gly Asp Thr Pro Leu His
 355 360 365
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 370 375 380
 Leu Thr Arg Lys Gly Ser Leu Leu Asn Glu Lys Asn Lys Ala Phe Leu
 385 390 395 400
 Thr Pro Leu His Leu Ala Ala Glu Leu Leu His Tyr Asp Ala Met Glu
 405 410 415
 Val Leu Leu Lys Gln Gly Ala Lys Val Asn Ala Leu Asp Ser Leu Gly
 420 425 430
 Gln Thr Pro Leu His Arg Cys Ala Arg Asp Glu Gln Ala Val Arg Leu
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 Leu Leu Ser Tyr Ala Ala Asp Thr Asn Ile Val Ser Leu Glu Gly Leu
 450 455 460
 Thr Ala Ala Gln Leu Ala Ser Asp Ser Val Leu Lys Leu Leu Lys Asn
 465 470 475 480
 Pro Pro Asp Ser Glu Thr His Leu Leu Glu Ala Ala Lys Ala Gly Asp
 485 490 495

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 Cys Arg Asp Leu Asp Gly Arg His Ser Thr Pro Leu His Phe Ala Ala
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 Gly Phe Asn Arg Val Pro Val Val Gln Phe Leu Leu Glu His Gly Ala
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 Glu Val Tyr Ala Ala Asp Lys Gly Gly Leu Val Pro Leu His Asn Ala
 545 550 555 560
 Cys Ser Tyr Gly His Tyr Glu Val Thr Glu Leu Leu Val Lys His Gly
 565 570 575
 Ala Asn Val Asn Val Ser Asp Leu Trp Lys Phe Thr Pro Leu His Glu
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 Ala Ala Ala Lys Gly Lys Tyr Asp Ile Cys Lys Leu Leu Leu Lys His
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 610 615 620
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 660 665 670
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 675 680 685
 Ala Glu Tyr Leu Leu Glu Asn Gly Ala Asp Val Asn Ala Gln Asp Lys
 690 695 700
 Gly Gly Leu Ile Pro Leu His Asn Ala Ser Ser Tyr Gly His Leu Asp
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 Ile Ala Ala Leu Leu Ile Lys His Lys Thr Val Val Asn Ala Thr Asp
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 Lys Trp Gly Phe Thr Pro Leu His Glu Ala Ala Gln Lys Gly Arg Thr
 740 745 750
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 755 760 765
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 770 775 780
 Lys Cys Leu Leu Gln Asp Ala Met Ala Thr Ser Leu Ser Gln Gln Ala
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 820 825 830
 Ile Leu Ser Pro Thr Thr Glu Thr Val Leu Leu Pro Thr Gly Ala Ser
 835 840 845
 Met Ile Leu Ser Val Pro Val Pro Leu Pro Leu Ser Ser Ser Thr Arg
 850 855 860

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Ile Ser Pro Ala Gln Gly Ala Glu Ala Asn Gly Ala Glu Gly Ser Ser
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 Phe Leu Ser Ser Gln Gln Leu His His Leu Ile Glu Leu Phe Glu Arg
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<400> 140
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<210> 141
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<212> DNA
<213> Artificial Sequence

<220>
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<210> 142
<211> 346
<212> DNA
<213> Homo sapiens

<400> 142
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tgcccaacagg cctgtggcaa aaggataaaa atgtgaacga agtttaacat tctgacttga 180
taaagcttta ataatgtaca gtgttttcta aatatttcct gttttttcag cactttaaca 240
gatgccattc cagggttaac tgggttgct gtactaaatt ataaacagag ttaacttgaa 300
ccttttatat gttatgcatt gattctaaca aactgtaatg ccctca 346

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<210> 144
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<220>
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ttaacagatg ccattccagg ttaaaactggg ttgtctgtac taaattataa acagagttaa 300
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tc 362

<210> 146

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<211> 5616

<212> DNA

<213> Homo sapiens

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<210> 147

<211> 29

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Primer

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<210> 148

<211> 34

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Primer

<400> 148

gccgaattcc ggctttgact tctctgaatt tagg

34

<210> 149

<211> 372

<212> DNA

<213> Homo sapiens

<400> 149

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372

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<210> 150
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 <213> Homo sapiens

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 Asp Gly Arg Asp Ala Asp Pro Thr Glu Glu Gln Met Ala Glu Thr Glu
 20 25 30
 aga aac gac gag gag cag ttc gaa tgc cag gaa ctg ctc gag tgc cag 144
 Arg Asn Asp Glu Glu Gln Phe Glu Cys Gln Glu Leu Leu Glu Cys Gln
 35 40 45
 gtg cag gtg ggg gcc ccc gag gag gag gag gag gag gag gag gac gcg 192
 Val Gln Val Val Gly Ala Pro Glu Glu Glu Glu Glu Glu Glu Asp Ala
 50 55 60
 ggc ctg gtg gcc gag gcc gag gcc gtg gct gcc ggc tgg atg ctc gat 240
 Gly Leu Val Ala Glu Ala Glu Ala Val Ala Ala Gly Trp Met Leu Asp
 65 70 75 80
 ttc ctc tgc ctc tct ctt tgc cga gct ttc cgc gac ggc cgc tcc gag 288
 Phe Leu Cys Leu Ser Leu Cys Arg Ala Phe Arg Asp Gly Arg Ser Glu
 85 90 95
 gac ttc cgc agg acc cgc aac agc gca gag gct att att cat gga cta 336
 Asp Phe Arg Arg Thr Arg Asn Ser Ala Glu Ala Ile Ile His Gly Leu
 100 105 110
 tcc agt cta aca gct tgc cag ttg aga acg ata tac ata tgt cag ttt 384
 Ser Ser Leu Thr Ala Cys Gln Leu Arg Thr Ile Tyr Ile Cys Gln Phe
 115 120 125
 ttg aca aga att gca gca gga aaa acc ctt gat gca cag ttt gaa aat 432
 Leu Thr Arg Ile Ala Ala Gly Lys Thr Leu Asp Ala Gln Phe Glu Asn
 130 135 140
 gat gaa cga att aca ccc ttg gaa tca gcc ctg atg att tgg ggt tca 480
 Asp Glu Arg Ile Thr Pro Leu Glu Ser Ala Leu Met Ile Trp Gly Ser
 145 150 155 160
 att gaa aag gaa cat gac aaa ctt cat gaa gaa ata cag aat tta att 528
 Ile Glu Lys Glu His Asp Lys Leu His Glu Glu Ile Gln Asn Leu Ile
 165 170 175
 aaa att cag gct ata gct gtt tgt atg gaa aat ggc aac ttt aaa gaa 576
 Lys Ile Gln Ala Ile Ala Val Cys Met Glu Asn Gly Asn Phe Lys Glu
 180 185 190
 gca gaa gaa gtc ttt gaa aga ata ttt ggt gat cca aat tct cat atg 624
 Ala Glu Glu Val Phe Glu Arg Ile Phe Gly Asp Pro Asn Ser His Met
 195 200 205
 cct ttc aaa agc aaa ttg ctt atg ata atc tct cag aaa gat aca ttt 672
 Pro Phe Lys Ser Lys Leu Met Ile Ile Ser Gln Lys Asp Thr Phe
 210 215 220
 cat tcc ttt ttt caa cac ttc agc tac aac cac atg atg gag aaa att 720
 His Ser Phe Phe Gln His Phe Ser Tyr Asn His Met Met Glu Lys Ile
 225 230 235 240

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aag agt tat gtg aat tat gtg cta agt gaa aaa tca tca acc ttt cta 768
Lys Ser Tyr Val Asn Tyr Val Leu Ser Glu Lys Ser Ser Thr Phe Leu
245 250 255

atg aag gca gcg gca aaa gta gta gaa agc aaa agg aca aga aca ata 816
Met Lys Ala Ala Ala Lys Val Val Glu Ser Lys Arg Thr Arg Thr Ile
260 265 270

act tct caa gat aaa cct agt ggt aat gat gtt gaa atg gaa act gaa 864
Thr Ser Gln Asp Lys Pro Ser Gly Asn Asp Val Glu Met Glu Thr Glu
275 280 285

gct aat ttg gat aca aga aaa agt gtt agt gac aaa cag tct gcg gta 912
Ala Asn Leu Asp Thr Arg Lys Ser Val Ser Asp Lys Gln Ser Ala Val
290 295 300

act gaa tcc tca gag ggt aca gta tcc tta ttg agg tct cac aag aat 960
Thr Glu Ser Ser Glu Gly Thr Val Ser Leu Leu Arg Ser His Lys Asn
305 310 315 320

ctt ttc tta tct aag ttg caa cat gga acc cag caa caa gac ctt aat 1008
Leu Phe Leu Ser Lys Leu Gln His Gly Thr Gln Gln Gln Asp Leu Asn
325 330 335

aag aaa gaa aga aga gta gga act cct caa agt aca aaa aag aaa aaa 1056
Lys Lys Glu Arg Arg Val Gly Thr Pro Gln Ser Thr Lys Lys Lys Lys
340 345 350

gaa agc aga aga gcc act gaa agc aga ata cct gtt tca aag agt cag 1104
Glu Ser Arg Arg Ala Thr Glu Ser Arg Ile Pro Val Ser Lys Ser Gln
355 360 365

ccg gta act cct gaa aaa cat cga gct aga aaa aga cag gca tgg ctt 1152
Pro Val Thr Pro Glu Lys His Arg Ala Arg Lys Arg Gln Ala Trp Leu
370 375 380

tgg gaa gaa gac aag aat ttg aga tct ggc gtg agg aaa tat gga gag 1200
Trp Glu Glu Asp Lys Asn Leu Arg Ser Gly Val Arg Lys Tyr Gly Glu
385 390 395 400

gga aac tgg tct aaa ata ctg ttg cat tat aaa ttc aac aac cgg aca 1248
Gly Asn Trp Ser Lys Ile Leu Leu His Tyr Lys Phe Asn Asn Arg Thr
405 410 415

agt gtc atg tta aaa gac aga tgg agg acc atg aag aaa cta aaa ctg 1296
Ser Val Met Leu Lys Asp Arg Trp Arg Thr Met Lys Lys Leu Lys Leu
420 425 430

att tcc tca gac agc gaa gac tga 1320
Ile Ser Ser Asp Ser Glu Asp
435

<210> 151

<211> 439

<212> PRT

<213> Homo sapiens

<400> 151

Met Ala Glu Asp Val Ser Ser Ala Ala Pro Ser Pro Arg Arg Cys Ala
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20 25 30

Arg Asn Asp Glu Glu Gln Phe Glu Cys Gln Glu Leu Leu Glu Cys Gln
35 40 45

Val Gln Val Gly Ala Pro Glu Glu Glu Glu Glu Glu Glu Asp Ala
50 55 60

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Gly Leu Val Ala Glu Ala Glu Ala Val Ala Ala Gly Trp Met Leu Asp
 65 70 75 80
 Phe Leu Cys Leu Ser Leu Cys Arg Ala Phe Arg Asp Gly Arg Ser Glu
 85 90 95
 Asp Phe Arg Arg Thr Arg Asn Ser Ala Glu Ala Ile Ile His Gly Leu
 100 105 110
 Ser Ser Leu Thr Ala Cys Gln Leu Arg Thr Ile Tyr Ile Cys Gln Phe
 115 120 125
 Leu Thr Arg Ile Ala Ala Gly Lys Thr Leu Asp Ala Gln Phe Glu Asn
 130 135 140
 Asp Glu Arg Ile Thr Pro Leu Glu Ser Ala Leu Met Ile Trp Gly Ser
 145 150 155 160
 Ile Glu Lys Glu His Asp Lys Leu His Glu Glu Ile Gln Asn Leu Ile
 165 170 175
 Lys Ile Gln Ala Ile Ala Val Cys Met Glu Asn Gly Asn Phe Lys Glu
 180 185 190
 Ala Glu Glu Val Phe Glu Arg Ile Phe Gly Asp Pro Asn Ser His Met
 195 200 205
 Pro Phe Lys Ser Lys Leu Leu Met Ile Ile Ser Gln Lys Asp Thr Phe
 210 215 220
 His Ser Phe Phe Gln His Phe Ser Tyr Asn His Met Met Glu Lys Ile
 225 230 235 240
 Lys Ser Tyr Val Asn Tyr Val Leu Ser Glu Lys Ser Ser Thr Phe Leu
 245 250 255
 Met Lys Ala Ala Ala Lys Val Val Glu Ser Lys Arg Thr Arg Thr Ile
 260 265 270
 Thr Ser Gln Asp Lys Pro Ser Gly Asn Asp Val Glu Met Glu Thr Glu
 275 280 285
 Ala Asn Leu Asp Thr Arg Lys Ser Val Ser Asp Lys Gln Ser Ala Val
 290 295 300
 Thr Glu Ser Ser Glu Gly Thr Val Ser Leu Leu Arg Ser His Lys Asn
 305 310 315 320
 Leu Phe Leu Ser Lys Leu Gln His Gly Thr Gln Gln Gln Asp Leu Asn
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 340 345 350
 Glu Ser Arg Arg Ala Thr Glu Ser Arg Ile Pro Val Ser Lys Ser Gln
 355 360 365
 Pro Val Thr Pro Glu Lys His Arg Ala Arg Lys Arg Gln Ala Trp Leu
 370 375 380
 Trp Glu Glu Asp Lys Asn Leu Arg Ser Gly Val Arg Lys Tyr Gly Glu
 385 390 395 400
 Gly Asn Trp Ser Lys Ile Leu Leu His Tyr Lys Phe Asn Asn Arg Thr
 405 410 415
 Ser Val Met Leu Lys Asp Arg Trp Arg Thr Met Lys Lys Leu Lys Leu
 420 425 430

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Ile Ser Ser Asp Ser Glu Asp
435

<210> 152

<211> 39

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Primer

<400> 152

gccccgggga tcctcatggc ggaggatgtt tcctcagcg 39

<210> 153

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Primer

<400> 153

tcccggggat cctcacacca ggcccgcgtc ctc 33

<210> 154

<211> 201

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)..(201)

<400> 154

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1 5 10 15

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Asp Gly Arg Asp Ala Asp Pro Thr Glu Glu Gln Met Ala Glu Thr Glu
20 25 30

aga aac gac gag gag cag ttc gaa tgc cag gaa ctg ctc gag tgc cag 144
Arg Asn Asp Glu Glu Gln Phe Glu Cys Gln Glu Leu Leu Glu Cys Gln
35 40 45

gtg cag gtg ggg gcc ccc gag gag gag gag gag gag gag gac gcg 192
Val Gln Val Gly Ala Pro Glu Glu Glu Glu Glu Glu Glu Asp Ala
50 55 60

ggc ctg gtg 201
Gly Leu Val
65

<210> 155

<211> 67

<212> PRT

<213> Homo sapiens

<400> 155

Met Ala Glu Asp Val Ser Ser Ala Ala Pro Ser Pro Arg Gly Cys Ala
1 5 10 15

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Asp Gly Arg Asp Ala Asp Pro Thr Glu Glu Gln Met Ala Glu Thr Glu
 20 25 30
 Arg Asn Asp Glu Glu Gln Phe Glu Cys Gln Glu Leu Leu Glu Cys Gln
 35 40 45
 Val Gln Val Gly Ala Pro Glu Glu Glu Glu Glu Glu Glu Asp Ala
 50 55 60
 Gly Leu Val
 65

<210> 156
 <211> 38
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:Primer

<400> 156
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<210> 157
 <211> 48
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:Primer

<400> 157
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<210> 158
 <211> 21
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:Primer

<400> 158
 gccgacttcg agtttgagca g 21

<210> 159
 <211> 1103
 <212> DNA
 <213> Homo sapiens

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 <221> CDS
 <222> (9)..(1094)

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 1 5 10
 gta tgt tct ctt ctc tta agt tat ggt gca gac cca aca ctg ctc aat 98
 Val Cys Ser Leu Leu Leu Ser Tyr Gly Ala Asp Pro Thr Leu Leu Asn
 15 20 25 30

-123-

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Cys His Asn Lys Ser Ala Ile Asp Leu Ala Pro Thr Pro Gln Leu Lys	
35 40 45	
gaa aga tta gca tat gaa ttt aaa ggc cac tcg ttg ctg caa gct gca	194
Glu Arg Leu Ala Tyr Glu Phe Lys Gly His Ser Leu Leu Gln Ala Ala	
50 55 60	
cga gaa gct gat gtt act cga atc aaa aaa cat ctc tct ctg gaa atg	242
Arg Glu Ala Asp Val Thr Arg Ile Lys Lys His Leu Ser Leu Glu Met	
65 70 75	
gtg aat ttc aag cat cct caa aca cat gaa aca gca ttg cat tgt gct	290
Val Asn Phe Lys His Pro Gln Thr His Glu Thr Ala Leu His Cys Ala	
80 85 90	
gct gca tct cca tat ccc aaa aga aag caa ata tgt gaa ctg ttg cta	338
Ala Ala Ser Pro Tyr Pro Lys Arg Lys Gln Ile Cys Glu Leu Leu Leu	
95 100 105 110	
aga aaa gga gca aac atc aat gaa aag act aaa gaa ttc ttg act cct	386
Arg Lys Gly Ala Asn Ile Asn Glu Lys Thr Lys Glu Phe Leu Thr Pro	
115 120 125	
ctg cac gtg gca tct gag aaa gct cat aat gat gtt gtt gaa gta gtg	434
Leu His Val Ala Ser Glu Lys Ala His Asn Asp Val Val Glu Val Val	
130 135 140	
gtg aaa cat gaa gca aag gtt aat gct ctg gat aat ctt ggt cag act	482
Val Lys His Glu Ala Lys Val Asn Ala Leu Asp Asn Leu Gly Gln Thr	
145 150 155	
tct cta cac aga gct gca tat tgt ggt cat cta caa acc tgc cgc cta	530
Ser Leu His Arg Ala Ala Tyr Cys Gly His Leu Gln Thr Cys Arg Leu	
160 165 170	
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Leu Leu Ser Tyr Gly Cys Asp Pro Asn Ile Ile Ser Leu Gln Gly Phe	
175 180 185 190	
act gct tta cag atg gga aat gaa aat gta cag caa ctc ctc caa gag	626
Thr Ala Leu Gln Met Gly Asn Glu Asn Val Gln Gln Leu Leu Gln Glu	
195 200 205	
ggt atc tca tta ggt aat tca gag gca gac aga caa ttg ctg gaa gct	674
Gly Ile Ser Leu Gly Asn Ser Glu Ala Asp Arg Gln Leu Leu Glu Ala	
210 215 220	
gca aag gct gga gat gtc gaa act gta aaa aaa ctg tgt act gtt cag	722
Ala Lys Ala Gly Asp Val Glu Thr Val Lys Lys Leu Cys Thr Val Gln	
225 230 235	
agt gtc aac tgc aga gac att gaa ggg cgt cag tct aca cca ctt cat	770
Ser Val Asn Cys Arg Asp Ile Glu Gly Arg Gln Ser Thr Pro Leu His	
240 245 250	
ttt gca gct ggg tat aac aga gtg tcc gtg gtg gaa tat ctg cta cag	818
Phe Ala Ala Gly Tyr Asn Arg Val Ser Val Val Glu Tyr Leu Leu Gln	
255 260 265 270	
cat gga gct gat gtg cat gct aaa gat aaa gga ggc ctt gta cct ttg	866
His Gly Ala Asp Val His Ala Lys Asp Lys Gly Gly Leu Val Pro Leu	
275 280 285	
cac aat gca tgt tct tat gga cat tat gaa gtt gca gaa ctt ctt gtt	914
His Asn Ala Cys Ser Tyr Gly His Tyr Glu Val Ala Glu Leu Leu Val	
290 295 300	

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aaa cat gga gca gta gtt aat gta gct gat tta tgg aaa ttt aca cct 962
Lys His Gly Ala Val Val Asn Val Ala Asp Leu Trp Lys Phe Thr Pro
      305              310              315

tta cat gaa gca gca gca aaa gga aaa tat gaa att tgc aaa ctt ctg 1010
Leu His Glu Ala Ala Ala Lys Gly Lys Tyr Glu Ile Cys Lys Leu Leu
      320              325              330

ctc cag cat ggt gca gac cct aca aaa aaa aac agg gat gga aat act 1058
Leu Gln His Gly Ala Asp Pro Thr Lys Lys Asn Arg Asp Gly Asn Thr
      335              340              345              350

cct ttg gat ctt gtt aaa gat gga gat aca gat att tagcggatc 1103
Pro Leu Asp Leu Val Lys Asp Gly Asp Thr Asp Ile
      355              360

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<210> 160
 <211> 362
 <212> PRT
 <213> Homo sapiens

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<400> 160
Phe Thr Pro Leu His Glu Ala Ala Ser Lys Asn Arg Val Glu Val Cys
 1          5          10          15

Ser Leu Leu Leu Ser Tyr Gly Ala Asp Pro Thr Leu Leu Asn Cys His
      20          25          30

Asn Lys Ser Ala Ile Asp Leu Ala Pro Thr Pro Gln Leu Lys Glu Arg
      35          40          45

Leu Ala Tyr Glu Phe Lys Gly His Ser Leu Leu Gln Ala Ala Arg Glu
      50          55          60

Ala Asp Val Thr Arg Ile Lys Lys His Leu Ser Leu Glu Met Val Asn
      65          70          75          80

Phe Lys His Pro Gln Thr His Glu Thr Ala Leu His Cys Ala Ala Ala
      85          90          95

Ser Pro Tyr Pro Lys Arg Lys Gln Ile Cys Glu Leu Leu Leu Arg Lys
      100          105          110

Gly Ala Asn Ile Asn Glu Lys Thr Lys Glu Phe Leu Thr Pro Leu His
      115          120          125

Val Ala Ser Glu Lys Ala His Asn Asp Val Val Glu Val Val Val Lys
      130          135          140

His Glu Ala Lys Val Asn Ala Leu Asp Asn Leu Gly Gln Thr Ser Leu
      145          150          155          160

His Arg Ala Ala Tyr Cys Gly His Leu Gln Thr Cys Arg Leu Leu Leu
      165          170          175

Ser Tyr Gly Cys Asp Pro Asn Ile Ile Ser Leu Gln Gly Phe Thr Ala
      180          185          190

Leu Gln Met Gly Asn Glu Asn Val Gln Gln Leu Leu Gln Glu Gly Ile
      195          200          205

Ser Leu Gly Asn Ser Glu Ala Asp Arg Gln Leu Leu Glu Ala Ala Lys
      210          215          220

Ala Gly Asp Val Glu Thr Val Lys Lys Leu Cys Thr Val Gln Ser Val
      225          230          235          240

Asn Cys Arg Asp Ile Glu Gly Arg Gln Ser Thr Pro Leu His Phe Ala
      245          250          255

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Ala Gly Tyr Asn Arg Val Ser Val Val Glu Tyr Leu Leu Gln His Gly
 260 265 270

Ala Asp Val His Ala Lys Asp Lys Gly Gly Leu Val Pro Leu His Asn
 275 280 285

Ala Cys Ser Tyr Gly His Tyr Glu Val Ala Glu Leu Leu Val Lys His
 290 295 300

Gly Ala Val Val Asn Val Ala Asp Leu Trp Lys Phe Thr Pro Leu His
 305 310 315 320

Glu Ala Ala Ala Lys Gly Lys Tyr Glu Ile Cys Lys Leu Leu Leu Gln
 325 330 335

His Gly Ala Asp Pro Thr Lys Lys Asn Arg Asp Gly Asn Thr Pro Leu
 340 345 350

Asp Leu Val Lys Asp Gly Asp Thr Asp Ile
 355 360

<210> 161

<211> 39

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Primer

<400> 161

cgtcgaccca tggcggagtc ttcggataag ctctatcga

39

<210> 162

<211> 39

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Primer

<400> 162

ggaaacgcgt ttggtgccag gatttactgt cagcttctt

39

<210> 163

<211> 39

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Primer

<400> 163

cttaaaccgcg ttgaaggaca aacaccttta gatttagtt

39

<210> 164

<211> 79

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Primer

<400> 164

gtcgaaagcg gccgcttagc ctccgaactg tggatgctc cacgtccat cgaccatacc 60
 ttcaggctc ataatctgg 79

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<210> 165
<211> 17
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 165
tttgttcgcc cagactc 17

<210> 166
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 166
tatgtttcag gttcaggggg ag 22

<210> 167
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 167
gcggaagctg gaggagtgc 20

<210> 168
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 168
gtcactcctc cagcttcgc 20

<210> 169
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 169
aagccctgaa gaagcagctc 20

<210> 170
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 170

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gagctgcttc ttcagggtt 20

<210> 171
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 171
cagacacca accggaagga 20

<210> 172
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 172
tccttcggt tgggtgtctg 20

<210> 173
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 173
tcgcctcca ccaagagcct 20

<210> 174
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 174
aggctcttg tggagcgga 20

<210> 175
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

<400> 175
tggcctggtg gacatcgta 20

<210> 176
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Primer

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<400> 176
taacgatgtc caccaggcca

20

<210> 177
<211> 3308
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Parp1a-Tank2b
Fusion

<220>
<221> CDS
<222> (1)..(3297)

<400> 177
atg aga ggc tcc cat cac cat cac cat cac gat tac gat atc cca acg 48
Met Arg Gly Ser His His His His His Asp Tyr Asp Ile Pro Thr
1 5 10 15
acc gaa aac ctg tat ttt cag ggc gcc atg gat ccg gaa ttc aaa ggc 96
Thr Glu Asn Leu Tyr Phe Gln Gly Ala Met Asp Pro Glu Phe Lys Gly
20 25 30
cta cgt cga ccc atg gcg gag tct tcg gat aag ctc tat cga gtc gag 144
Leu Arg Arg Pro Met Ala Glu Ser Ser Asp Lys Leu Tyr Arg Val Glu
35 40 45
tac gcc aag agc ggg cgc gcc tct tgc aag aaa tgt agc gag agc atc 192
Tyr Ala Lys Ser Gly Arg Ala Ser Cys Lys Lys Cys Ser Glu Ser Ile
50 55 60
ccc aag gac tcg ctc cgg atg gcc atc atg gtg cag tcg ccc atg ttt 240
Pro Lys Asp Ser Leu Arg Met Ala Ile Met Val Gln Ser Pro Met Phe
65 70 75 80
gat gga aaa gtc cca cac tgg tac cac ttc tcc tgc ttc tgg aag gtg 288
Asp Gly Lys Val Pro His Trp Tyr His Phe Ser Cys Phe Trp Lys Val
85 90 95
ggc cac tcc atc cgg cac cct gac gtt gag gtg gat ggg ttc tct gag 336
Gly His Ser Ile Arg His Pro Asp Val Glu Val Asp Gly Phe Ser Glu
100 105 110
ctt cgg tgg gat gac cag cag aaa gtc aag aag aca gcg gaa gct gga 384
Leu Arg Trp Asp Asp Gln Gln Lys Val Lys Lys Thr Ala Glu Ala Gly
115 120 125
gga gtg aca ggc aaa ggc cag gat gga att ggt agc aag gca gag aag 432
Gly Val Thr Gly Lys Gly Gln Asp Gly Ile Gly Ser Lys Ala Glu Lys
130 135 140
act ctg ggt gac ttt gca gca gag tat gtc aag tcc aac aga agt acg 480
Thr Leu Gly Asp Phe Ala Ala Glu Tyr Val Lys Ser Asn Arg Ser Thr
145 150 155 160
tgc aag ggg tgt atg gag aag ata gaa aag ggc cag gtg cgc ctg tcc 528
Cys Lys Gly Cys Met Glu Lys Ile Glu Lys Gly Gln Val Arg Leu Ser
165 170 175
aag aag atg gtg gac ccg gag aag cca cag cta ggc atg att gac cgc 576
Lys Lys Met Val Asp Pro Glu Lys Pro Gln Leu Gly Met Ile Asp Arg
180 185 190
tgg tac cat cca ggc tgc ttt gtc aag aac agg gag gag ctg ggt ttc 624
Trp Tyr His Pro Gly Cys Phe Val Lys Asn Arg Glu Glu Leu Gly Phe
195 200 205

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cgg ccc gag tac agt gcg agt cag ctc aag ggc ttc agc ctc ctt gct	672
Arg Pro Glu Tyr Ser Ala Ser Gln Leu Lys Gly Phe Ser Leu Leu Ala	
210 215 220	
aca gag gat aaa gaa gcc ctg aag aag cag ctc cca gga gtc aag agt	720
Thr Glu Asp Lys Glu Ala Leu Lys Lys Gln Leu Pro Gly Val Lys Ser	
225 230 235 240	
gaa gga aag aga aaa ggc gat gag gtg gat gga gtg gat gaa gtg gcg	768
Glu Gly Lys Arg Lys Gly Asp Glu Val Asp Gly Val Asp Glu Val Ala	
245 250 255	
aag aag aaa tct aaa aaa gaa aaa gac aag gat agt aag ctt gaa aaa	816
Lys Lys Lys Ser Lys Lys Glu Lys Asp Lys Asp Ser Lys Leu Glu Lys	
260 265 270	
gcc cta aag gct cag aac gac ctg atc tgg aac atc aag gac gag cta	864
Ala Leu Lys Ala Gln Asn Asp Leu Ile Trp Asn Ile Lys Asp Glu Leu	
275 280 285	
aag aaa gtg tgt tca act aat gac ctg aag gag cta ctc atc ttc aac	912
Lys Lys Val Cys Ser Thr Asn Asp Leu Lys Glu Leu Leu Ile Phe Asn	
290 295 300	
aag cag caa gtg cct tct ggg gag tcg gcg atc ttg gac cga gta gct	960
Lys Gln Gln Val Pro Ser Gly Glu Ser Ala Ile Leu Asp Arg Val Ala	
305 310 315 320	
gat ggc atg gtg ttc ggt gcc ctc ctt ccc tgc gag gaa tgc tcg ggt	1008
Asp Gly Met Val Phe Gly Ala Leu Leu Pro Cys Glu Glu Cys Ser Gly	
325 330 335	
cag ctg gtc ttc aag agc gat gcc tat tac tgc act ggg gac gtc act	1056
Gln Leu Val Phe Lys Ser Asp Ala Tyr Tyr Cys Thr Gly Asp Val Thr	
340 345 350	
gcc tgg acc aag tgt atg gtc aag aca cag aca ccc aac cgg aag gag	1104
Ala Trp Thr Lys Cys Met Val Lys Thr Gln Thr Pro Asn Arg Lys Glu	
355 360 365	
tgg gta acc cca aag gaa ttc cga gaa atc tct tac ctc aag aaa ttg	1152
Trp Val Thr Pro Lys Glu Phe Arg Glu Ile Ser Tyr Leu Lys Lys Leu	
370 375 380	
aag gtt aaa aag cag gac cgt ata ttc ccc cca gaa acc agc gcc tcc	1200
Lys Val Lys Lys Gln Asp Arg Ile Phe Pro Pro Glu Thr Ser Ala Ser	
385 390 395 400	
gtg gcg gcc acg cct ccg ccc tcc aca gcc tcg gct cct gct gct gtg	1248
Val Ala Ala Thr Pro Pro Pro Ser Thr Ala Ser Ala Pro Ala Ala Val	
405 410 415	
aac tcc tct gct tca gca gat aag cca tta tcc aac atg aag atc ctg	1296
Asn Ser Ser Ala Ser Ala Asp Lys Pro Leu Ser Asn Met Lys Ile Leu	
420 425 430	
act ctc ggg aag ctg tcc cgg aac aag gat gaa gtg aag gcc atg att	1344
Thr Leu Gly Lys Leu Ser Arg Asn Lys Asp Glu Val Lys Ala Met Ile	
435 440 445	
gag aaa ctc ggg ggg aag ttg acg ggg acg gcc aac aag gct tcc ctg	1392
Glu Lys Leu Gly Gly Lys Leu Thr Gly Thr Ala Asn Lys Ala Ser Leu	
450 455 460	
tgc atc agc acc aaa aag gag gtg gaa aag atg aat aag aag atg gag	1440
Cys Ile Ser Thr Lys Lys Glu Val Glu Lys Met Asn Lys Lys Met Glu	
465 470 475 480	

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gaa gta aag gaa gcc aac atc cga gtt	gtg tct gag gac ttc ctc cag	1488
Glu Val Lys Glu Ala Asn Ile Arg Val	Val Ser Glu Asp Phe Leu Gln	
485	490 495	
gac gtc tcc gcc tcc acc aag agc ctt	cag gag ttg ttc tta gcg cac	1536
Asp Val Ser Ala Ser Thr Lys Ser	Gln Glu Leu Phe Leu Ala His	
500	505 510	
atc ttg tcc cct tgg ggg gca gag gtg	aag gca gag cct gtt gaa gtt	1584
Ile Leu Ser Pro Trp Gly Ala Val	Lys Ala Glu Pro Val Glu Val	
515	520 525	
gtg gcc cca aga ggg aag tca ggg gct	gcg ctc tcc aaa aaa agc aag	1632
Val Ala Pro Arg Gly Lys Ser Gly	Ala Ala Leu Ser Lys Lys Ser Lys	
530	535 540	
ggc cag gtc aag gag gaa ggt atc aac	aaa tct gaa aag aga atg aaa	1680
Gly Gln Val Lys Glu Glu Gly Ile Asn	Lys Ser Glu Lys Arg Met Lys	
545	550 555 560	
tta act ctt aaa gga gga gca gct gtg	gat cct gat tct gga ctg gaa	1728
Leu Thr Leu Lys Gly Gly Ala Ala Val	Asp Pro Asp Ser Gly Leu Glu	
565	570 575	
cac tct gcg cat gtc ctg gag aaa ggt	ggg aag gtc ttc agt gcc acc	1776
His Ser Ala His Val Leu Glu Lys Gly	Gly Lys Val Phe Ser Ala Thr	
580	585 590	
ctt ggc ctg gtg gac atc gtt aaa gga	acc aac tcc tac tac aag ctg	1824
Leu Gly Leu Val Asp Ile Val Lys Gly	Thr Asn Ser Tyr Tyr Lys Leu	
595	600 605	
cag ctt ctg gag gac gac aag gaa aac	agg tat tgg ata ttc agg tcc	1872
Gln Leu Leu Glu Asp Asp Lys Glu Asn	Arg Tyr Trp Ile Phe Arg Ser	
610	615 620	
tgg ggc cgt gtg ggt acg gtg atc ggt	agc aac aaa ctg gaa cag atg	1920
Trp Gly Arg Val Gly Thr Val Ile Gly	Ser Asn Lys Leu Glu Gln Met	
625	630 635 640	
ccg tcc aag gag gat gcc att gag cac	ttc atg aaa tta tat gaa gaa	1968
Pro Ser Lys Glu Asp Ala Ile Glu His	Phe Met Lys Leu Tyr Glu Glu	
645	650 655	
aaa acc ggg aac gct tgg cac tcc aaa	aat ttc acg aag tat ccc aaa	2016
Lys Thr Gly Asn Ala Trp His Ser Lys	Asn Phe Thr Lys Tyr Pro Lys	
660	665 670	
aag ttc tac ccc ctg gag att gac tat	ggc cag gat gaa gag gca gtg	2064
Lys Phe Tyr Pro Leu Glu Ile Asp Tyr	Gly Gln Asp Glu Glu Ala Val	
675	680 685	
aag aag ctg aca gta aat cct ggc acc	aaa cgc gtt gaa gga caa aca	2112
Lys Lys Leu Thr Val Asn Pro Gly Thr	Lys Arg Val Glu Gly Gln Thr	
690	695 700	
cct tta gat tta gtt tca gca gat gat	gtc agc gct ctt ctg aca gca	2160
Pro Leu Asp Leu Val Ser Ala Asp Asp	Val Ser Ala Leu Leu Thr Ala	
705	710 715 720	
gcc atg ccc cca tct gct ctg ccc tct	tgt tac aag cct caa gtg ctc	2208
Ala Met Pro Pro Ser Ala Leu Pro Ser	Cys Tyr Lys Pro Gln Val Leu	
725	730 735	
aat ggt gtg aga agc cca gga gcc act	gca gat gct ctc tct tca ggt	2256
Asn Gly Val Arg Ser Pro Gly Ala Thr	Ala Asp Ala Leu Ser Ser Gly	
740	745 750	

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cca tct agc cca tca agc ctt tct gca gcc agc agt ctt gac aac tta	2304
Pro Ser Ser Pro Ser Ser Leu Ser Ala Ala Ser Ser Leu Asp Asn Leu	
755 760 765	
tct ggg agt ttt tca gaa ctg tct tca gta gtt agt tca agt gga aca	2352
Ser Gly Ser Phe Ser Glu Ser Ser Val Val Ser Ser Ser Gly Thr	
770 775 780	
gag ggt gct tcc agt ttg gag aaa aag gag gtt cca gga gta gat ttt	2400
Glu Gly Ala Ser Ser Glu Lys Lys Glu Val Pro Gly Val Asp Phe	
785 790 795 800	
agc ata act caa ttc gta agg aat ctt gga ctt gag cac cta atg gat	2448
Ser Ile Thr Gln Phe Val Arg Asn Leu Gly Leu Glu His Leu Met Asp	
805 810 815	
ata ttt gag aga gaa cag atc act ttg gat gta tta gtt gag atg ggg	2496
Ile Phe Glu Arg Glu Gln Ile Thr Leu Asp Val Leu Val Glu Met Gly	
820 825 830	
cac aag gag ctg aag gag att gga atc aat gct tat gga cat agg cac	2544
His Lys Glu Leu Lys Glu Ile Gly Ile Asn Ala Tyr Gly His Arg His	
835 840 845	
aaa cta att aaa gga gtc gag aga ctt atc tcc gga caa caa ggt ctt	2592
Lys Leu Ile Lys Gly Val Glu Arg Leu Ile Ser Gly Gln Gln Gly Leu	
850 855 860	
aac cca tat tta act ttg aac acc tct ggt agt gga aca att ctt ata	2640
Asn Pro Tyr Leu Thr Leu Asn Thr Ser Gly Ser Gly Thr Ile Leu Ile	
865 870 875 880	
gat ctg tct cct gat gat aaa gag ttt cag tct gtg gag gaa gag atg	2688
Asp Leu Ser Pro Asp Asp Lys Glu Phe Gln Ser Val Glu Glu Glu Met	
885 890 895	
caa agt aca gtt cga gag cac aga gat gga ggt cat gca ggt gga atc	2736
Gln Ser Thr Val Arg Glu His Arg Asp Gly Gly His Ala Gly Gly Ile	
900 905 910	
ttc aac aga tac aat att ctc aag att cag aag gtt tgt aac aag aaa	2784
Phe Asn Arg Tyr Asn Ile Leu Lys Ile Gln Lys Val Cys Asn Lys Lys	
915 920 925	
cta tgg gaa aga tac act cac cgg aga aaa gaa gtt tct gaa gaa aac	2832
Leu Trp Glu Arg Tyr Thr His Arg Arg Lys Glu Val Ser Glu Glu Asn	
930 935 940	
cac aac cat gcc aat gaa cga atg cta ttt cat ggg tct cct ttt gtg	2880
His Asn His Ala Asn Glu Arg Met Leu Phe His Gly Ser Pro Phe Val	
945 950 955 960	
aat gca att atc cac aaa ggc ttt gat gaa agg cat gcg tac ata ggt	2928
Asn Ala Ile Ile His Lys Gly Phe Asp Glu Arg His Ala Tyr Ile Gly	
965 970 975	
ggt atg ttt gga gct ggc att tat ttt gct gaa aac tct tcc aaa agc	2976
Gly Met Phe Gly Ala Gly Ile Tyr Phe Ala Glu Asn Ser Ser Lys Ser	
980 985 990	
aat caa tat gta tat gga att gga gga ggt act ggg tgt cca gtt cac	3024
Asn Gln Tyr Val Tyr Gly Ile Gly Gly Gly Thr Gly Cys Pro Val His	
995 1000 1005	
aaa gac aga tct tgt tac att tgc cac agg cag ctg ctc ttt tgc cgg	3072
Lys Asp Arg Ser Cys Tyr Ile Cys His Arg Gln Leu Leu Phe Cys Arg	
1010 1015 1020	

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gta acc ttg gga aag tct ttc ctg cag ttc agt gca atg aaa atg gca 3120
Val Thr Leu Gly Lys Ser Phe Leu Gln Phe Ser Ala Met Lys Met Ala
1025 1030 1035 1040

cat tct cct cca ggt cat cac tca gtc act ggt agg ccc agt gta aat 3168
His Ser Pro Gly His His Ser Val Thr Gly Arg Pro Ser Val Asn
1045 1050 1055

ggc cta gca tta gct gaa tat gtt att tac aga gga gaa cag gct tat 3216
Gly Leu Ala Leu Ala Glu Tyr Val Ile Tyr Arg Gly Glu Gln Ala Tyr
1060 1065 1070

cct gag tat tta att act tac cag att atg agg cct gaa ggt atg gtc 3264
Pro Glu Tyr Leu Ile Thr Tyr Gln Ile Met Arg Pro Glu Gly Met Val
1075 1080 1085

gat gga gcg tgg agg cat cca cag ttc gga ggc taagcggccg c 3308
Asp Gly Ala Trp Arg His Pro Gln Phe Gly Gly
1090 1095

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<210> 178

<211> 1099

<212> PRT

<213> Artificial Sequence

<223> Description of Artificial Sequence:Parpla-Tank2b
Fusion

<400> 178

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Met Arg Gly Ser His His His His His Asp Tyr Asp Ile Pro Thr
 1          5          10          15

Thr Glu Asn Leu Tyr Phe Gln Gly Ala Met Asp Pro Glu Phe Lys Gly
          20          25          30

Leu Arg Arg Pro Met Ala Glu Ser Ser Asp Lys Leu Tyr Arg Val Glu
          35          40          45

Tyr Ala Lys Ser Gly Arg Ala Ser Cys Lys Lys Cys Ser Glu Ser Ile
          50          55          60

Pro Lys Asp Ser Leu Arg Met Ala Ile Met Val Gln Ser Pro Met Phe
          65          70          75          80

Asp Gly Lys Val Pro His Trp Tyr His Phe Ser Cys Phe Trp Lys Val
          85          90          95

Gly His Ser Ile Arg His Pro Asp Val Glu Val Asp Gly Phe Ser Glu
          100          105          110

Leu Arg Trp Asp Asp Gln Gln Lys Val Lys Lys Thr Ala Glu Ala Gly
          115          120          125

Gly Val Thr Gly Lys Gly Gln Asp Gly Ile Gly Ser Lys Ala Glu Lys
          130          135          140

Thr Leu Gly Asp Phe Ala Ala Glu Tyr Val Lys Ser Asn Arg Ser Thr
          145          150          155          160

Cys Lys Gly Cys Met Glu Lys Ile Glu Lys Gly Gln Val Arg Leu Ser
          165          170          175

Lys Lys Met Val Asp Pro Glu Lys Pro Gln Leu Gly Met Ile Asp Arg
          180          185          190

Trp Tyr His Pro Gly Cys Phe Val Lys Asn Arg Glu Glu Leu Gly Phe
          195          200          205

Arg Pro Glu Tyr Ser Ala Ser Gln Leu Lys Gly Phe Ser Leu Leu Ala
          210          215          220

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Thr Glu Asp Lys Glu Ala Leu Lys Lys Gln Leu Pro Gly Val Lys Ser
 225 230 235 240
 Glu Gly Lys Arg Lys Gly Asp Glu Val Asp Gly Val Asp Glu Val Ala
 245 250 255
 Lys Lys Lys Ser Lys Lys Glu Lys Asp Lys Asp Ser Lys Leu Glu Lys
 260 265 270
 Ala Leu Lys Ala Gln Asn Asp Leu Ile Trp Asn Ile Lys Asp Glu Leu
 275 280 285
 Lys Lys Val Cys Ser Thr Asn Asp Leu Lys Glu Leu Leu Ile Phe Asn
 290 295 300
 Lys Gln Gln Val Pro Ser Gly Glu Ser Ala Ile Leu Asp Arg Val Ala
 305 310 315 320
 Asp Gly Met Val Phe Gly Ala Leu Leu Pro Cys Glu Glu Cys Ser Gly
 325 330 335
 Gln Leu Val Phe Lys Ser Asp Ala Tyr Tyr Cys Thr Gly Asp Val Thr
 340 345 350
 Ala Trp Thr Lys Cys Met Val Lys Thr Gln Thr Pro Asn Arg Lys Glu
 355 360 365
 Trp Val Thr Pro Lys Glu Phe Arg Glu Ile Ser Tyr Leu Lys Lys Leu
 370 375 380
 Lys Val Lys Lys Gln Asp Arg Ile Phe Pro Pro Glu Thr Ser Ala Ser
 385 390 395 400
 Val Ala Ala Thr Pro Pro Ser Thr Ala Ser Ala Pro Ala Ala Val
 405 410 415
 Asn Ser Ser Ala Ser Ala Asp Lys Pro Leu Ser Asn Met Lys Ile Leu
 420 425 430
 Thr Leu Gly Lys Leu Ser Arg Asn Lys Asp Glu Val Lys Ala Met Ile
 435 440 445
 Glu Lys Leu Gly Gly Lys Leu Thr Gly Thr Ala Asn Lys Ala Ser Leu
 450 455 460
 Cys Ile Ser Thr Lys Lys Glu Val Glu Lys Met Asn Lys Lys Met Glu
 465 470 475 480
 Glu Val Lys Glu Ala Asn Ile Arg Val Val Ser Glu Asp Phe Leu Gln
 485 490 495
 Asp Val Ser Ala Ser Thr Lys Ser Leu Gln Glu Leu Phe Leu Ala His
 500 505 510
 Ile Leu Ser Pro Trp Gly Ala Glu Val Lys Ala Glu Pro Val Glu Val
 515 520 525
 Val Ala Pro Arg Gly Lys Ser Gly Ala Ala Leu Ser Lys Lys Ser Lys
 530 535 540
 Gly Gln Val Lys Glu Glu Gly Ile Asn Lys Ser Glu Lys Arg Met Lys
 545 550 555 560
 Leu Thr Leu Lys Gly Gly Ala Ala Val Asp Pro Asp Ser Gly Leu Glu
 565 570 575
 His Ser Ala His Val Leu Glu Lys Gly Gly Lys Val Phe Ser Ala Thr
 580 585 590

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Leu Gly Leu Val Asp Ile Val Lys Gly Thr Asn Ser Tyr Tyr Lys Leu
 595 600 605
 Gln Leu Leu Glu Asp Asp Lys Glu Asn Arg Tyr Trp Ile Phe Arg Ser
 610 615 620
 Trp Gly Arg Val Gly Thr Val Ile Gly Ser Asn Lys Leu Glu Gln Met
 625 630 635 640
 Pro Ser Lys Glu Asp Ala Ile Glu His Phe Met Lys Leu Tyr Glu Glu
 645 650 655
 Lys Thr Gly Asn Ala Trp His Ser Lys Asn Phe Thr Lys Tyr Pro Lys
 660 665 670
 Lys Phe Tyr Pro Leu Glu Ile Asp Tyr Gly Gln Asp Glu Glu Ala Val
 675 680 685
 Lys Lys Leu Thr Val Asn Pro Gly Thr Lys Arg Val Glu Gly Gln Thr
 690 695 700
 Pro Leu Asp Leu Val Ser Ala Asp Asp Val Ser Ala Leu Leu Thr Ala
 705 710 715 720
 Ala Met Pro Pro Ser Ala Leu Pro Ser Cys Tyr Lys Pro Gln Val Leu
 725 730 735
 Asn Gly Val Arg Ser Pro Gly Ala Thr Ala Asp Ala Leu Ser Ser Gly
 740 745 750
 Pro Ser Ser Pro Ser Ser Leu Ser Ala Ala Ser Ser Leu Asp Asn Leu
 755 760 765
 Ser Gly Ser Phe Ser Glu Leu Ser Ser Val Val Ser Ser Ser Gly Thr
 770 775 780
 Glu Gly Ala Ser Ser Leu Glu Lys Lys Glu Val Pro Gly Val Asp Phe
 785 790 795 800
 Ser Ile Thr Gln Phe Val Arg Asn Leu Gly Leu Glu His Leu Met Asp
 805 810 815
 Ile Phe Glu Arg Glu Gln Ile Thr Leu Asp Val Leu Val Glu Met Gly
 820 825 830
 His Lys Glu Leu Lys Glu Ile Gly Ile Asn Ala Tyr Gly His Arg His
 835 840 845
 Lys Leu Ile Lys Gly Val Glu Arg Leu Ile Ser Gly Gln Gln Gly Leu
 850 855 860
 Asn Pro Tyr Leu Thr Leu Asn Thr Ser Gly Ser Gly Thr Ile Leu Ile
 865 870 875 880
 Asp Leu Ser Pro Asp Asp Lys Glu Phe Gln Ser Val Glu Glu Glu Met
 885 890 895
 Gln Ser Thr Val Arg Glu His Arg Asp Gly Gly His Ala Gly Gly Ile
 900 905 910
 Phe Asn Arg Tyr Asn Ile Leu Lys Ile Gln Lys Val Cys Asn Lys Lys
 915 920 925
 Leu Trp Glu Arg Tyr Thr His Arg Arg Lys Glu Val Ser Glu Glu Asn
 930 935 940
 His Asn His Ala Asn Glu Arg Met Leu Phe His Gly Ser Pro Phe Val
 945 950 955 960

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Asn Ala Ile Ile His Lys Gly Phe Asp Glu Arg His Ala Tyr Ile Gly
965 970 975

Gly Met Phe Gly Ala Gly Ile Tyr Phe Ala Glu Asn Ser Ser Lys Ser
980 985 990

Asn Gln Tyr Val Tyr Gly Ile Gly Gly Gly Thr Gly Cys Pro Val His
995 1000 1005

Lys Asp Arg Ser Cys Tyr Ile Cys His Arg Gln Leu Leu Phe Cys Arg
1010 1015 1020

Val Thr Leu Gly Lys Ser Phe Leu Gln Phe Ser Ala Met Lys Met Ala
1025 . 1030 1035 1040

His Ser Pro Pro Gly His His Ser Val Thr Gly Arg Pro Ser Val Asn
1045 1050 1055

Gly Leu Ala Leu Ala Glu Tyr Val Ile Tyr Arg Gly Glu Gln Ala Tyr
1060 1065 1070

Pro Glu Tyr Leu Ile Thr Tyr Gln Ile Met Arg Pro Glu Gly Met Val
1075 1080 1085

Asp Gly Ala Trp Arg His Pro Gln Phe Gly Gly
1090 1095

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/17827

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/54 C12N9/10 C07K16/40 C12Q1/68 C12Q1/48
 A61K38/45 //A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 15647 A (GARVAN INST MED RES ;SUTHERLAND ROBERT LYND SAY (AU); DALY ROGER JO) 1 April 1999 (1999-04-01) page 8 -page 10, line 24 page 13 -page 17 ---	7
A	SMITH S ET AL: "Tankyrase, a poly(ADP-ribose) polymerase at human telomeres" SCIENCE, vol. 282, no. 5393, 20 November 1998 (1998-11-20), pages 1484-1487, XP002118903 ISSN: 0036-8075 cited in the application --- -/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

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- *8* document member of the same patent family

Date of the actual completion of the international search

5 December 2000

Date of mailing of the international search report

11/12/2000

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/17827

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 61813 A (FUNK WALTER D ;MORIN GREGG B (US); GERON CORP (US); PIATYSZEK MIEC) 19 October 2000 (2000-10-19) page 2, line 9 -page 3, line 15 examples claims figure 4	1,3,4, 6-17, 19-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/17827

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9915647 A	01-04-1999	AU 9245898 A EP 1017802 A	12-04-1999 12-07-2000
WO 0061813 A	19-10-2000	NONE	

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